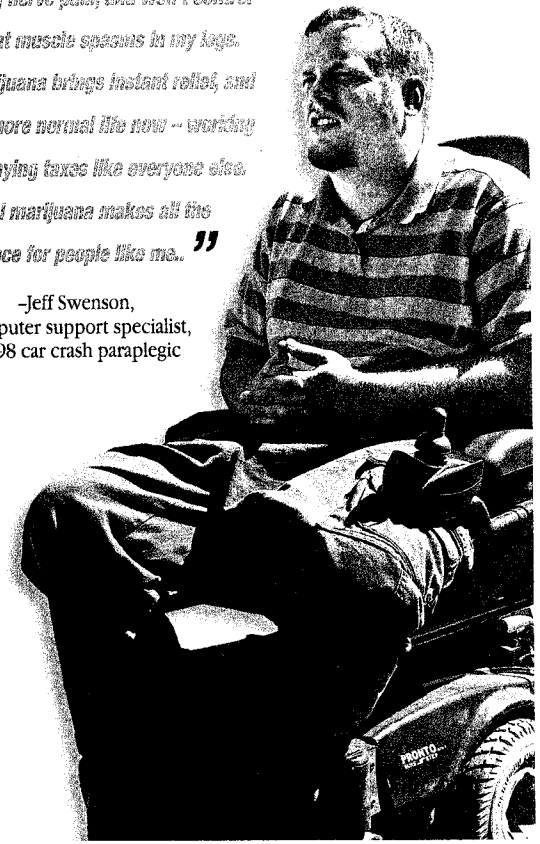
Medical marijuana, proven by modern research, benefits a wide range of conditions:

- Cancer
- Glaucoma
- HIV (AIDS)
- Wasting Syndrome (Cachexia)
- Chronic Pain
- Severe Pain
- Migraines
- Nausea
- Seizures
- Epilepsy
- Muscle Spasms
- Multiple Sclerosis
- Crohn's Disease
- Inflammation
- Arthritis
- Rheumatism
- Fibromyalgia
- Osteoporosis
- Diabetes
- Alzheimer's Disease
- Lou Gehrig's Disease
- Tourette's Syndrome
- Hepatitis C
- Hypertension
- Depression & Bipolar Disorder
- Sleep Apnea

....and more

"Even tons of Oxycontin can't cut my never-ending nerve pain, and won't control the constant muscle spasms in my legs. Medical marijuana brings instant relief, and I can live a more normal life now -- working full-time, paying taxes like everyone else. Medical marijuana makes all the difference for people like me."

-Jeff Swenson,
computer support specialist,
1998 car crash paraplegic



Montana's Medical Marijuana Act, passed by 62% of voters in 2004, allows physicians to make medical marijuana recommendations to patients diagnosed with certain conditions and symptoms. The law (M.C.A. 50-46) also protects physicians and indemnifies them from liability.

patients & families united is a network of Montana patients and their loved ones working together to improve each other's lives and to publicize the facts about medical marijuana. We conduct public education programs targeting everyone, especially healthcare providers, law enforcement agencies and public officials. Most people don't know that the peer-reviewed published literature about medical marijuana, including double-blind studies, is voluminous. The pace of new global research increases every year, as do the breadth and significance of the research findings.

This brochure highlights just a few illustrative examples of marijuana's benefits to patients suffering from conditions both severe and common. The studies cited or mentioned - some focused on the full marijuana flower, others focused on specific constituents unique to marijuana - demonstrate how marijuana is proven to be safe and effective medicine. This research mirrors the experiences of the thousands of patients in the growing number of states that allow the use of medical marijuana.

Learn more at our website - **www.mtmjpatients.org** - which features timely news as well as links to some of the world's leading web-based resources and published research about medical marijuana.

patients & families united

P.O. Box 1471
Helena, Montana 59624
www.mtmjpatients.org
info@mtmjpatients.org

PUBLIC HEALTH, WELFARE & SAFETY
Exhibit No. 3
Date 2-6-09
Bill No. SB 326

The Medical Uses of Marijuana

"... safer than most medicines prescribed every day. If marijuana were a new discovery rather than a well-known substance carrying cultural and political baggage, it would be hail"

-Lester Grin
emeritus pr
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PUBLIC HEALTH, WELFARE & SAFETY
Exhibit No. 3
Date 2-6-09
Bill No. SB 326

modern research confirms thousands of years of anecdotal and historical evidence–

medical marijuana produces dramatic beneficial effects.

Safer than Most Medicines Prescribed Every Day

Modern research documents that marijuana compares favorably to other medicines. It is not physically addictive. It presents fewer side effects - of dramatically lesser consequence and risk - than opioids and numerous other commonly prescribed pharmaceuticals. Many patients report dramatic reductions in their need for other riskier and more expensive prescribed drugs when using medical marijuana. After literally thousands of years of continuous use by peoples of all cultures and eras, there exists not a single recorded incident of death or overdose caused by marijuana.

Marijuana Helps Cancer Patients

Numerous double-blind studies document marijuana's remarkable value in addressing the symptoms of cancer and the side-effects of cancer-treatment, like pain, nausea and low-appetite. Many people are unaware that other research has documented instances of medical marijuana actually *shrinking* cancerous tumors. Lifelong cigarette smokers who also smoke marijuana have even been found to have a *lower* risk of lung cancer than smokers who don't also use marijuana. And chronic marijuana smokers get cancer no more often than people who have never smoked marijuana or cigarettes.

> *"Cannabinoids – the active components of Cannabis sativa and their derivatives – exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating appetite. In addition, these compounds have been shown to inhibit the growth of tumor cells… Cannabinoids are usually well tolerated, and do not produce the generalized toxic effects of conventional chemotherapies."*

–Guzman, 2003. Cannabinoids: potential anticancer agents. *Nature Reviews: Cancer.* Volume 3, October 2003.

Marijuana Relieves Pain

Name the cause and type of pain, and chances are that recent double-blind research and/or decades of anecdotal information from patients shows that medical marijuana provides effective relief. This includes chronic pain resulting from severe injuries and conditions such as fibromyalgia, Multiple Sclerosis, cancer and neuropathy related to diabetes, HIV and other conditions. Where pain is connected to inflammation, research has found that medical marijuana delivers site-specific anti-inflammatory relief. Most patients report that marijuana doesn't reduce their ability to function normally the way opiates do, and that they can reduce dramatically or even eliminate their need for opiates and similar risky pain-relievers when using marijuana.

Marijuana Reduces Suffering from Rheumatoid Arthritis

Double-blind research documents that medical marijuana significantly improves pain on movement, pain at rest, quality of sleep, inflammation, and intensity of pain. Other research has found that marijuana effectively blocks the progression of arthritis.

> *"effectively blocked [the] progression of arthritis"*

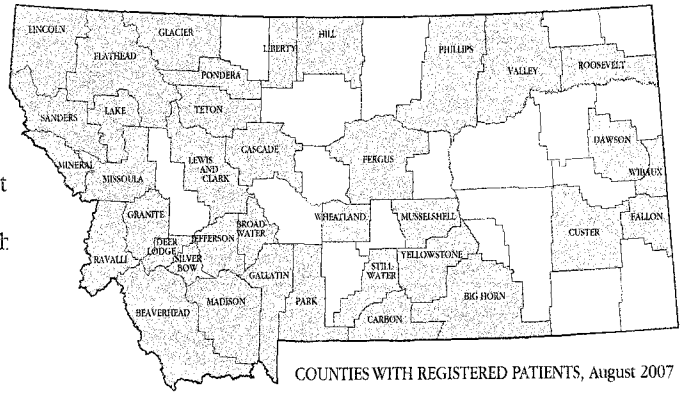
–Malfait et al. 2000. The nonpsychoacticannabis constituents cannabidiol is an oral anti-arthritic therapeutic in murine. *Journal of the Proceedings of the National Academy of Sciences* 97: 9561-9566.

Marijuana Slows & Alleviates Multiple Sclerosis

Clinical studies show that marijuana may inhibit the progression of MS. Numerous studies document medical marijuana's power in addressing the disease's many unrelenting symptoms - including pain, muscle spasms, depression, fatigue, and incontinence.

> *"The results of this study are important because they suggest that in addition to symptom management, …cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in Multiple Sclerosis and probably other diseases."*

–Pryce et al. 2003. Cannabinoids inhibit neurodegeneration in models of Multiple Sclerosis. *Brain* 126: 2191-2202.



COUNTIES WITH REGISTERED PATIENTS, August 2007

Smoking *Not* Required

Research documents that vaporizers eliminate completely the negative effects of smoking. Patients also can administer medical marijuana by eating it cooked in many ways - in butter, cakes, cookies, sauces, etc. Patients report medicinal benefits from drinking medical marijuana in teas and from administering via compress or tincture. **Smoking *isn't the only way*** to receive this medicine - but smoking or vaporizing are the easiest ways for patients to feel beneficial effects almost immediately, and to realize their greatest ability to make delicate adjustments in dosage.

Marijuana in Pills and Other Forms

Marinol - consists solely of THC (tetrahydracannabinol), one of more than 66 known medicinally-active compounds in marijuana. It is approved by U.S. Food & Drug Administration (FDA) only for nausea-reduction and appetite-stimulation, and research suggests that it does little - and may be counterproductive - when used for pain relief. Most patients report effects decidedly inferior to those of medical marijuana or of products derived from the full marijuana flower. And Marinol costs considerably more: a typical one-month prescription costs up to $1,200, while equivalent marijuana ranges from virtually free when grown by oneself, up to approximately $500 on the open market.

Sativex - a liquid distilled from the full marijuana flower, species-and-content-controlled, administered in controlled dosages via spray. Currently approved for physician prescription in Canada; approval pending in Europe; just beginning clinical trials in the U.S. under FDA protocols in 2007. Cost expected to be significantly higher than marijuana plants.

Varieties & Strains - Just as there are different kinds of apples and tomatoes, so too for the marijuana plant; and different strains in the genus *cannabis* offer different medicinal advantages. Patients typically research and share information to learn which strains will best meet their needs.

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Select Endorsers of Medical MJ Access

- The American Academy of HIV Medicine
- American College of Physicians
- Leukemia & Lymphoma Society
- The American Nurses Association
- The American Public Health Association
- The American Society of Addiction Medicine
- American Academy of Addiction Psychiatry
- Arthritis Research Campaign
- British Medical Association
- HIV Medicine Association of the Infectious Diseases Society of America
- The Lymphoma Foundation of America
- The National Association for Public Health Policy
- The National Nurses Society on Addictions
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- The United Methodist Church's Board of Church and Society
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"[Marijuana is] safer than most medicines prescribed every day. If marijuana were a new discovery rather than a well-known substance carrying cultural and political baggage, it would be hailed as a wonder drug."

--Dr. Lester Grinspoon
Harvard Medical School
professor emeritus,
co-author of *Marijuana: The Forbidden Medicine*

"[Marijuana] effectively blocked the progression of arthritis."

--Malfait et al. 2000.

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"The results of this study are important because they suggest that in addition to symptom management... cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in Multiple Sclerosis and probably other diseases."

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"Cannabinoids – the active components of Cannabis sativa and their derivatives – exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating appetite. In addition, these compounds have been shown to inhibit the growth of tumor cells… Cannabinoids are usually well tolerated, and do not produce the generalized toxic effects of conventional chemotherapies."

--Guzman, 2003.

Cannabinoids: potential anti-cancer agents.

Nature Reviews: Cancer
Volume 3, October 2003.

"The clinical potential of cannabinoids is large; some people suggest that cannabis could be the 'aspirin of the 21st century'.... Cannabinoids inhibit pain in virtually every experimental pain paradigm."

--Ware, M. A. et al. 2003.

The Therapeutic Potential of Cannabis.

The Lancet Neurology,
May 2003.

SB 326

nature

Vol 435|23 June 2005|doi:10.1038/nature03658

LETTERS

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An endocannabinoid mechanism for stress-induced analgesia

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Acute stress suppresses pain by activating brain pathways that engage opioid or non-opioid mechanisms. Here we show that an opioid-independent form of this phenomenon, termed stress-induced analgesia[1], is mediated by the release of endogenous marijuana-like (cannabinoid) compounds in the brain. Blockade of cannabinoid CB_1 receptors in the periaqueductal grey matter of the midbrain prevents non-opioid stress-induced analgesia. In this region, stress elicits the rapid formation of two endogenous cannabinoids, the lipids 2-arachidonoylglycerol[2] (2-AG) and anandamide[3]. A newly developed inhibitor of the 2-AG-deactivating enzyme, monoacylglycerol lipase[4,5], selectively increases 2-AG concentrations and, when injected into the periaqueductal grey matter, enhances stress-induced analgesia in a CB_1-dependent manner. Inhibitors of the anandamide-deactivating enzyme fatty-acid amide hydrolase[6], which selectively elevate anandamide concentrations, exert similar effects. Our results indicate that the coordinated release of 2-AG and anandamide in the periaqueductal grey matter might mediate opioid-independent stress-induced analgesia. These studies also identify monoacylglycerol lipase as a previously unrecognized therapeutic target.

Stress activates neural systems that inhibit pain sensation. This adaptive response, referred to as stress-induced analgesia (SIA), depends on the recruitment of brain pathways that project from the amygdala to the midbrain periaqueductal grey matter (PAG) and descend to the brainstem rostroventromedial medulla and dorsal horn of the spinal cord[7]. Endogenous opioid peptides have key functions in this process[1,8], but other as yet unidentified neurotransmitters are also known to be involved[1]. We proposed that endocannabinoids might be implicated in stress analgesia for two reasons. First, agonists of CB_1 receptors—the predominant cannabinoid receptor subtype present in the brain[9,10]—exert profound antinociceptive effects[7] and suppress activity in nociceptive neurons[11–14]. Second, CB_1 antagonists increase the activity of nociceptive rostroventromedial medulla neurons[14] and enhance sensitivity to noxious stimuli[15], indicating that an intrinsic endocannabinoid tone might regulate descending antinociceptive pathways[7].

To study non-opioid SIA we delivered brief, continuous electric foot shock to rats and quantified their sensitivity to pain after stress by using the tail-flick test. As demonstrated previously[1,16], this stimulation protocol caused a profound antinociceptive effect that was not affected by intraperitoneal (i.p.) injection of the opiate antagonist naltrexone ($14\,mg\,kg^{-1}$) (Fig. 1a). However, the response was almost abolished by administration of the CB_1 antagonist rimonabant (SR141617A, $5\,mg\,kg^{-1}$ i.p.) (Fig. 1a) or its analogue AM251 ($5\,mg\,kg^{-1}$ i.p.) (Supplementary Fig. 1), but not by the CB_2 antagonist SR144528 ($5\,mg\,kg^{-1}$ i.p.) (Fig. 1a). The effects of CB_1 antagonists cannot be attributed to changes in basal nociceptive threshold because, in the absence of the stressor, the drugs failed to alter tail-flick latencies (Supplementary Figs 1 and 2).

If CB_1 activation is required for the expression of non-opioid SIA, the latter should be lower in animals rendered tolerant to the

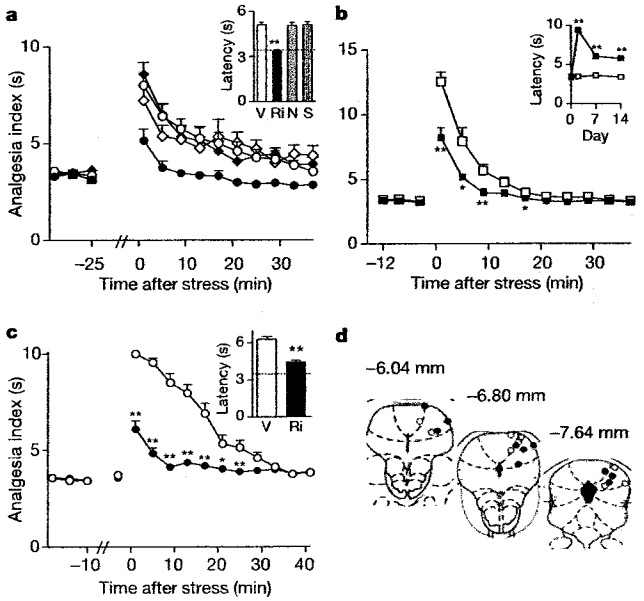

Figure 1 | CB_1 receptors mediate non-opioid stress-induced analgesia. **a**, CB_1 antagonist rimonabant (Ri, filled circles) blocks stress antinociception. Opiate antagonist naltrexone (N, open diamonds) and CB_2 antagonist SR144528 (S, filled diamonds) have no effect. Open circles, vehicle (V). Inset: drug effects ($F_{3,29} = 5.99$, $P < 0.003$). The dotted line indicates the nociceptive threshold. Analgesia index was measured as the tail-flick latency. **b**, Stress antinociception is attenuated in WIN55212-2-tolerant rats (filled squares) compared with controls (open squares) ($F_{1,19} = 16.74$, $P < 0.0007$). Inset: non-stress cannabinoid antinociception is attenuated in WIN55212-2-tolerant rats ($F_{2,38} = 35.11$, $P < 0.0002$). **c**, Rimonabant in dorsolateral PAG suppresses stress antinociception ($F_{10,170} = 20.01$, $P < 0.0002$). Inset: drug effects ($F_{1,17} = 25.63$, $P < 0.0002$). **d**, PAG injection sites. Error bars, where visible, indicate s.e.m.; $n = 6$–11 per group. Asterisk, $P < 0.05$; two asterisks, $P < 0.01$ (analysis of variance, Fisher's PLSD test).

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antinociceptive effects of cannabinoids. Consistent with this prediction, rats chronically treated with the cannabinoid agonist WIN55212-2 (10 mg kg^{-1} i.p., once daily for 14 days) displayed, along with the expected blunting of acute CB_1-dependent antinociception (Fig. 1b, inset), a marked decrease in stress antinociception (Fig. 1b). The possibility that this decrement might be due to changes in opioid tone is unlikely for two reasons: first, rats tolerant to WIN55212-2 showed no deficit in their antinociceptive response to morphine (2.5 mg kg^{-1} subcutaneously) (data not shown); and second, in accord with previous results[16], rats tolerant to morphine (10 mg kg^{-1} subcutaneously once daily for 7 days) showed normal non-opioid stress antinociception (Supplementary Fig. 3).

The PAG serves key functions in both the descending control of pain[7,17] and the antinociceptive actions of cannabinoid agonists[18]. We therefore asked whether blockade of CB_1 receptors in this structure could affect SIA. Rimonabant (2 nmol) reduced stress antinociception when microinjected into the dorsolateral PAG (Fig. 1c, d), a structure linked to non-opioid stimulation-produced analgesia[17,19], but was inactive after injection into the lateral and ventrolateral PAG (Supplementary Fig. 4). The antagonist was also ineffective when administered into the lateral ventricle, indicating that its actions were not due to diffusion to distal sites (Supplementary Fig. 5). These results are consistent with the presence of CB_1 receptors throughout the dorsal midbrain[9,20] and indicate that endocannabinoid release and/or intrinsic CB_1 receptor activity in the PAG might contribute to SIA.

To determine whether endocannabinoid release participates in this response, we measured anandamide and 2-AG concentrations in the dorsal midbrain of rats killed before (nonshock) or at various times after foot shock (Supplementary Fig. 6). Liquid chromatography/mass spectrometry (LC–MS) analyses revealed that midbrain 2-AG concentrations were markedly increased 2 min after shock termination and returned to baseline about 15 min later (Fig. 2a). This response preceded a sustained increase in anandamide concentration, which peaked 7–15 min after foot shock (Fig. 2a). No such changes were observed in the occipital cortex (Fig. 2b), a brain region that contains CB_1 receptors[9] but is not considered part of the SIA circuit.

The rapid accumulation of 2-AG in the midbrain after stress indicates that endocannabinoid release, rather than intrinsic CB_1 activity, might be responsible for SIA. If this is so, selective inhibitors of the 2-AG-hydrolysing enzyme monoacylglycerol lipase (MGL) should heighten the intrinsic actions of 2-AG and enhance its analgesic effects. The absence of selective MGL inhibitors prompted us to develop such an agent. To develop MGL-specific inhibitors we started from the assumption that similarities should exist between the substrate-binding site of MGL and that of the anandamide-hydrolysing enzyme fatty-acid amide hydrolase (FAAH)[6]: the fact that both hydrolases cleave arachidonic-acid derivatives indicates that their binding pockets might accommodate inhibitors of similar bulk and hydrophobicity. We therefore examined a collection of carbamate derivatives in which selective FAAH inhibition had been achieved by mimicking the flexible acyl chain of anandamide with the isosteric, but more rigid, biphenyl group (Fig. 3a)[21,22]. This screening revealed that although *O*-biphenyl carbamates (Fig. 3a: **1**, URB597; **2**, URB524) inhibit the activity of FAAH but not that of MGL, *N*-biphenyl carbamates (Fig. 3a, **3**, URB602) display an opposite selectivity (Fig. 3b, c). URB602 inhibited rat brain MGL with a half-maximal concentration (IC_{50}) of 28 ± 4 μM (Fig. 3b) through a noncompetitive mechanism. Without URB602, the apparent Michaelis constant (K_m) of MGL for 2-AG was 24.0 ± 1.7 μM and the maximum velocity (V_{max}) was 1814 ± 51 nmol min per mg protein; with URB602, the K_m was 20.0 ± 0.4 μM and the V_{max} was 541 ± 20 nmol min per mg protein ($n = 4$). When organotypic slice

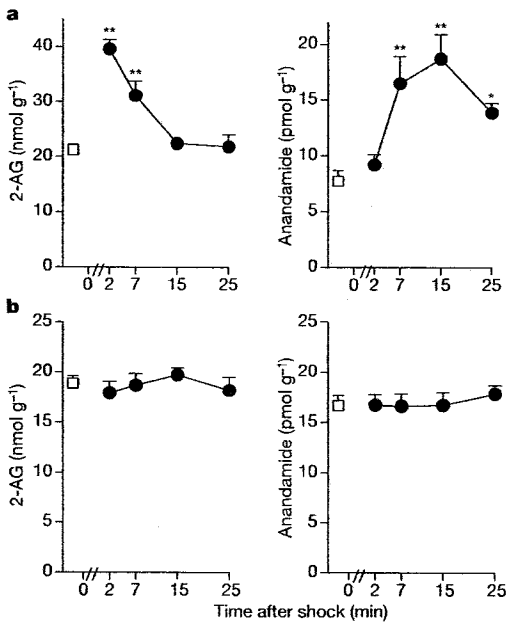

Figure 2 | Stress stimulates the formation of 2-AG and anandamide in dorsal midbrain. Non-stress (open squares) and post-stress (filled circles) concentrations of 2-AG and anandamide in dorsal midbrain samples containing the entire PAG (**a**) and in occipital cortex samples (**b**). Error bars indicate s.e.m.; $n = 10$ per group. Asterisk, $P < 0.05$ compared with non-stressed controls; two asterisks, $P < 0.01$.

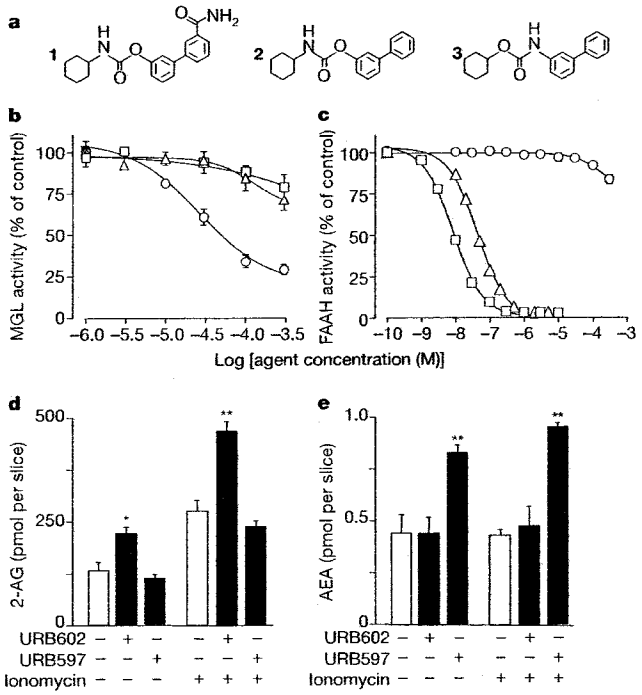

Figure 3 | URB602 is a selective MGL inhibitor. **a**, Structures of *O*-biphenyl-substituted FAAH inhibitors (**1**, URB597; **2**, URB524) and the *N*-biphenyl-substituted MGL inhibitor URB602 (**3**). **b**, URB602 (circles) inhibits rat brain MGL activity, whereas URB597 (squares) and URB524 (triangles) have no such effect. **c**, URB602 does not affect rat brain FAAH activity, which is suppressed by URB597 and URB524. **d**, **e**, URB602 (100 μM) increases the concentration of 2-AG (**d**) but not of anandamide (**e**) in rat brain slice cultures. Effects of ionomycin (2 μM) and URB597 (1 μM) are also shown. Asterisk, $P < 0.05$; two asterisks, $P < 0.01$ versus control, *t*-test ($n = 4$). Error bars indicate s.e.m.

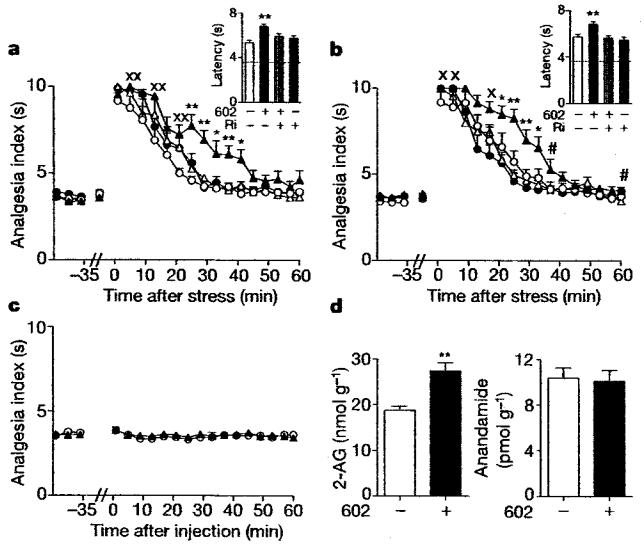

Figure 4 | The MGL inhibitor URB602 enhances non-opioid stress-induced analgesia. **a**, **b**, URB602 (602) increases stress antinociception when microinjected in dorsolateral PAG (**a**) and lateral/ventrolateral PAG (**b**), but does not cause antinociception in non-stressed rats (lateral/ventrolateral PAG) (**c**). Rimonabant blocks these effects. Open circles, vehicle; filled triangles, URB602; filled circles, rimonabant; open triangles, URB602/rimonabant. Analgesia index was measured as the tail-flick latency. Insets: drug effects (**a**, $F_{3,26} = 7.39$, $P < 0.002$; **b**, $F_{3,25} = 9.15$, $P < 0.0004$). Dotted lines indicate nociceptive thresholds. **d**, URB602 in the ventrolateral PAG increases the concentration of 2-AG, but not of anandamide, measured 25 min after shock. Error bars indicate s.e.m.; $n = 6$–10 per group. Asterisk, $P < 0.05$ compared with all groups; two asterisks, $P < 0.01$; cross, $P < 0.05$ compared with vehicle; two crosses, $P < 0.01$; hash, $P < 0.05$ compared with URB602/rimonabant; ANOVA, Fisher's PLSD post-hoc test.

cultures of rat forebrain were incubated with URB602 (100 μM), both baseline and Ca^{2+}-ionophore-stimulated 2-AG concentrations were increased (Fig. 3d). In contrast, URB602 did not change anandamide content (Fig. 3e), which was markedly elevated by the FAAH inhibitor URB597 (ref. 21) at 1 μM (Fig. 3e). Moreover, URB602 did not affect the activities of lipid-metabolizing enzymes such as diacylglycerol lipase[23] and cyclooxygenase-2 (ref. 24) and did not significantly influence binding of [^{3}H]WIN55212-2 to CB_1 or CB_2 receptors ($IC_{50} \geq 5$ μM) or [^{35}S]GTP-γS to rat cerebellar membranes (half-maximal effective concentration (EC_{50}) > 50 μM) (Supplementary Table 1, and data not shown).

Because of its relatively low potency, URB602 is not suitable for systemic administration. Nevertheless, microinjections of the MGL inhibitor (0.1 nmol) into the dorsolateral PAG (Supplementary Fig. 7a) or lateral/ventrolateral PAG (Supplementary Fig. 7b) enhanced stress-induced antinociception (Fig. 4a, b). Basal nociceptive thresholds in non-shocked rats were unaffected (Fig. 4c; Supplementary Fig. 7c). This effect was probably due to the accumulation of 2-AG in the PAG, for three reasons. First, it was prevented by the simultaneous administration of rimonabant (0.2 nmol) (Fig. 4a, b). Second, it was mimicked by the non-selective MGL inhibitor methyl arachidonyl fluorophosphonate[5] (2.6 nmol), whose effects also were blocked by rimonabant (Supplementary Fig. 9). Last, it was accompanied by an increase in midbrain 2-AG concentration: 25 min after foot shock, when the antinociceptive effect of URB602 was at its peak (Fig. 4a, b), 2-AG content was significantly higher in midbrain fragments of URB602-treated rats relative to vehicle-treated controls (Fig. 4d). Anandamide concentrations were identical in the two groups (Fig. 4d), further highlighting the selectivity of URB602 for MGL. These results indicate that URB602 is a selective MGL inhibitor that enhances stress antinociception.

To examine the possible role of anandamide in SIA, we administered the FAAH inhibitor URB597 (ref. 21) either by systemic (0.3 mg kg^{-1}, i.p) (Fig. 5a) or local (0.1 nmol) (Fig. 5b; Supplementary Fig. 8) injection into the dorsolateral PAG. In both cases URB597 caused a potentiation of stress antinociception, which was prevented by rimonabant (1 mg kg^{-1} i.p.; 0.2 nmol in the PAG) (Fig. 5a, b). The FAAH inhibitor did not modify basal nociceptive thresholds (Fig. 5a, b). Furthermore, administration of the anandamide transport inhibitor VDM11 (10 mg kg^{-1} i.p.)[25] exerted similar effects, which also were blocked by rimonabant (2 mg kg^{-1} i.p.) (Fig. 5c).

Our results indicate that the concerted release of 2-AG and anandamide in the PAG might mediate non-opioid SIA. The two endocannabinoids might act on local CB_1 receptors[9,20,26] to regulate

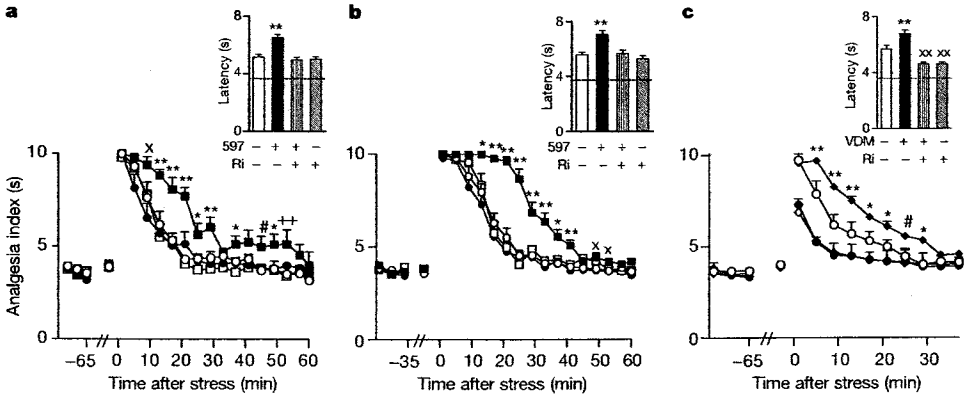

Figure 5 | Inhibitors of anandamide hydrolysis (URB597) and transport (VDM11) enhance non-opioid stress-induced analgesia. URB597 (filled squares) administered systemically (**a**) or in dorsolateral PAG (**b**) and VDM11 (filled diamonds) administered systemically (**c**) potentiate stress antinociception. Rimonabant blocks these effects after systemic administration (**a**, 1 mg kg^{-1}; **c**, 2 mg kg^{-1}) or administration in PAG (**b**). Vehicle, open circles; rimonabant, filled circles, URB597/rimonabant, open squares; VDM11/rimonabant, open diamonds. Analgesia index was measured as the tail-flick latency. Insets: effects of URB597 (**a**, $F_{3,28} = 11.56$, $P < 0.0002$; **b**, $F_{3,24} = 33.69$, $P < 0.0002$) and VDM11 (**c**, $F_{3,26} = 21.76$, $P < 0.0002$). Error bars indicate s.e.m.; $n = 5$–9 per group. Asterisk, $P < 0.05$ compared with all groups; two asterisks, $P < 0.01$; cross, $P < 0.05$ compared with vehicle; two crosses, $P < 0.01$; hash, $P < 0.05$ compared with rimonabant (ANOVA, Fisher's PLSD post-hoc test). Dotted lines indicate nociceptive thresholds.

glutamate- and GABA-mediated transmission, ultimately disinhibiting descending pain control pathways. Three points are noteworthy. First, endocannabinoid-dependent stress antinociception is not affected by opioid antagonists or morphine tolerance, implying that it might not require opioid activity. The reverse may not be true, however, because mutant CB_1-null mice have reduced opioid-mediated responses to stress[27]. Second, the residual antinociception observed in the presence of CB_1 antagonists leaves open the possibility that additional mediators of SIA remain to be discovered. Last, stress triggers the formation of both 2-AG and anandamide in the midbrain, but these two endocannabinoids are released with strikingly dissimilar time-courses. This observation underscores the existence of functional differences between these signalling molecules[28], pointing to the possibility that they might act in a coordinated manner to modulate temporally and/or spatially distinct processes in the PAG and other brain regions. The ability of both MGL and FAAH inhibitors to magnify endocannabinoid-dependent SIA also highlights the significance of these enzymes as previously undescribed targets for the treatment of pain and stress-related disorders.

METHODS

Chemicals. We synthesized URB597, URB524 and [$^2H_4$]anandamide as described[21,22,29,30], and URB602 (biphenyl-3-yl carbamic acid cyclohexyl ester) by reacting diimidazole-1-ylmethanone with biphenyl-3-yl amine in acetonitrile in the presence of 4-dimethylaminopyridine and subsequently with cyclohexanol. Other chemicals were obtained and administered as described in Supplementary Methods.

Animals. We used adult male Sprague–Dawley rats for *in vivo* experiments and Wistar rats for enzyme assays and tissue cultures. All procedures were approved by the institutional animal care and use committee and followed guidelines of the International Association for the Study of Pain.

Brain slice cultures. We cultured brain slices from Wistar rats. Pups were killed on postnatal day 5 by decapitation after cryo-anaesthesia. Brains were removed and cut (0.4-mm-thick coronal slices) with a vibratome in a bath of ice-cold high-glucose DMEM (Gibco). Hemispheres were placed on Millicell culture inserts (Millipore) in six-well plates with serum-based culture medium (1.5 ml) composed of basal Eagle's medium with Earle's salts (100 ml), Earle's balanced salt solution (50 ml), heat-inactivated horse serum (50 ml), L-glutamine (0.2 mM, 1 ml) and 50% glucose (2 ml) (all from Gibco). Slices were maintained at 37 °C with 5% CO_2 for 7 days before use.

Lipid extractions and LC–MS analyses. For *ex vivo* experiments, we habituated rats to the guillotine for at least 7 days before the experiment and killed them either before or at various times (2, 7, 15 and 25 min) after a 3-min foot shock ($n = 10$ per group). The brains were rapidly removed, dissected and stored frozen (−80 °C) until lipid extraction. For *in vitro* experiments, we removed the medium of slice cultures and replaced it with DMEM (1 ml) containing URB602 (100 μM), URB597 (1 μM) or vehicle (0.1% dimethylsulphoxide) and incubated the slices at 25 °C for 10 min. In some experiments, slices were incubated with ionomycin (2 μM) in DMEM for a further 15 min. Reactions were stopped and washed with ice-cold 50% methanol (1 ml). Slices were collected in the same medium (0.2 ml) and homogenized. Brain tissue (about 50 mg) and slice homogenates were suspended in methanol (2 ml) including ^2H-containing internal standards (25 pmol). Lipids were extracted in methanol/chloroform/water (1:2:0.25). The organic phase was recovered, evaporated to dryness, reconstituted in chloroform/methanol (1:3, 80 μl) and subjected to LC–MS analysis as described[30].

Enzyme assays. We prepared cell fractions from Wistar rat brain homogenates, and assayed cytosol MGL activity and membrane FAAH activity with 2-monooleoyl[1,2,3-^3H]glycerol (ARC; 20 Ci mmol^{-1}), and [ethanolamine-^3H] anandamide (ARC; 60 Ci mmol^{-1}), respectively, as substrates[4,21].

Surgery and tolerance induction. We implanted stainless-steel guide cannulae in the PAG (dorsolateral or lateral/ventrolateral) or left lateral ventricle under pentobarbital/ketamine anaesthesia 3–7 days before testing. Placements of cannulae were verified in Nissl-stained sections or by post-mortem injection of fast green dye. Analyses were restricted to animals exhibiting dye spread throughout the ventricular system. The induction of tolerance to WIN55212-2 and morphine is described in Supplementary Methods.

Assessment of antinociception. We administered foot shock (0.9 mA, alternating current, for 3 min) to Sprague–Dawley rats with a Lafayette grid-shock apparatus. Withdrawal latencies in the radiant-heat tail-flick test[13,17] were measured at 2-min intervals before (baseline) and after foot shock, and calculated for each subject in two-trial blocks. Removal of the tail from the heat source terminated the application of thermal stimulation. Tail-flick latencies were monitored for 4 min immediately before exposure to the stressor to evaluate changes in nociceptive thresholds induced by pharmacological manipulations. Ceiling tail-flick latencies were 10 s except where noted. Tail-flick latencies, measured at baseline or before administration of the stressor, did not differ between groups in any study.

Data analyses. We analysed results with analysis of variance (ANOVA), repeated-measures ANOVA and Fisher's protected least-significant-difference post-hoc tests. $P < 0.05$ was considered significant.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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The endogenous cannabinoid system controls extinction of aversive memories

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Acquisition and storage of aversive memories is one of the basic principles of central nervous systems throughout the animal kingdom[1]. In the absence of reinforcement, the resulting behavioural response will gradually diminish to be finally extinct. Despite the importance of extinction[2], its cellular mechanisms are largely unknown. The cannabinoid receptor 1 (CB1)[3] and endocannabinoids[4] are present in memory-related brain areas[5,6] and modulate memory[7,8]. Here we show that the endogenous cannabinoid system has a central function in extinction of aversive memories. CB1-deficient mice showed strongly impaired short-term and long-term extinction in auditory fear-conditioning tests, with unaffected memory acquisition and consolidation. Treatment of wild-type mice with the CB1 antagonist SR141716A mimicked the phenotype of CB1-deficient mice, revealing that CB1 is required at the moment of memory extinction. Consistently, tone presentation during extinction trials resulted in elevated levels of endocannabinoids in the basolateral amygdala complex, a region known to control extinction of aversive memories[9]. In the basolateral amygdala, endocannabinoids and CB1 were crucially involved in long-term depression of GABA (γ-aminobutyric acid)-mediated inhibitory currents. We propose that endocannabinoids facilitate extinction of aversive memories through their selective inhibitory effects on local inhibitory networks in the amygdala.

To study the involvement of the endogenous cannabinoid system in memory processing, we generated CB1-deficient mice ($CB1^{-/-}$; see Supplementary Information). $CB1^{-/-}$ mice and $CB1^{+/+}$ littermates were tested in auditory fear conditioning, which is highly dependent on the amygdala[1] and enables the dissection of different phases of memory formation, including acquisition, consolidation and extinction. Mice were trained to associate a tone with a foot-shock (conditioning). After conditioning, animals froze when

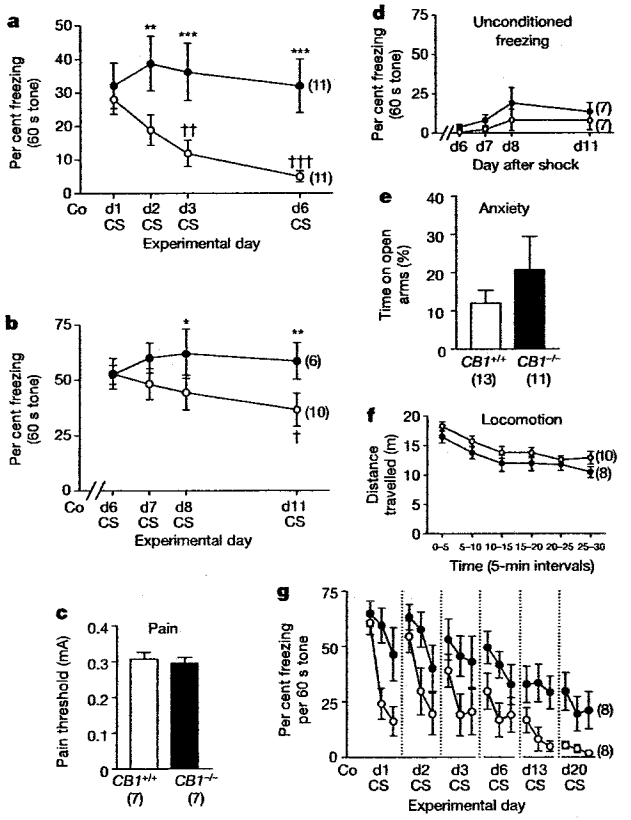

Figure 1 Impaired extinction of aversive memory in an auditory fear-conditioning task of $CB1^{-/-}$ mice (filled circles) as compared to their $CB1^{+/+}$ littermates (open circles). **a**, **b**, After conditioning (Co) animals were repeatedly exposed to 60 s tones (conditioned stimulus, CS) starting 24 h after conditioning (**a**) (d1) or after a 6-day consolidation period (**b**) (d6). **c**–**f**, $CB1^{-/-}$ and $CB1^{+/+}$ mice did not differ in their sensory-motor abilities, as assessed by sensitivity to rising electric foot-shock (**c**), unspecific freezing to a tone after shock application (**d**), anxiety-related behaviour on the elevated plus maze (**e**) and horizontal locomotion in an open field (**f**). **g**, $CB1^{-/-}$ mice showed memory extinction in response to a stronger extinction protocol (3 min tones until day 20; analysed in 60-s intervals), but still froze more than $CB1^{+/+}$ controls. Means ± s.e.m. are shown; number of animals are indicated in parentheses. Asterisk, $P < 0.05$; double asterisk, $P < 0.01$; triple asterisk, $P < 0.001$ (compared with $CB1^{+/+}$); dagger, $P < 0.05$; double dagger, $P < 0.01$; triple dagger, $P < 0.001$ (compared with day 1).

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re-exposed to the tone. This response served as an indicator of aversive memory, and is gradually extinguished on repeated tone presentations. As the amygdala has a crucial role for extinction of aversive memories[9,10], we studied amygdala-dependent memory performance in the absence of possible confounding influences of the hippocampus by re-exposing the mice to the tone in an environment different from the conditioning context[1]. In this environment, neither $CB1^{-/-}$ nor $CB1^{+/+}$ mice showed freezing without tone presentation 24 h after conditioning (data not shown). During the subsequent tone presentation, however, animals of both groups showed the same amount of freezing (Fig. 1a; d1, $P > 0.05$), pointing to an equally successful tone–foot-shock association. On repeated exposure to the tone, however, $CB1^{+/+}$ and $CB1^{-/-}$ mice differed significantly in their freezing behaviour (genotype: $F_{1,20} = 5.81$, $P < 0.05$; genotype × day interaction: $F_{3,60} = 4.86$, $P < 0.005$; Fig. 1a). In fact, $CB1^{+/+}$ mice ($F_{3,10} = 9.70$, $P < 0.0005$), but not $CB1^{-/-}$ ($F_{3,10} = 0.94$, $P = 0.433$), showed extinction of freezing.

The identical behavioural performance of the two genotypes on day 1 indicates that acquisition and early consolidation processes do not involve CB1. However, it is possible that memory consolidation processes were not completed 24 h after conditioning, leaving open a potential involvement of CB1 in later phases of memory consolidation. To test this hypothesis, new groups of animals remained undisturbed after conditioning for 6 days, and mice from these groups were then exposed to the 60-s tones (Fig. 1b). Again, $CB1^{-/-}$ and $CB1^{+/+}$ mice did not differ in their initial freezing response, but behaved in a significantly different way in the course of repeated tone presentations (genotype × day interaction: $F_{3,42} = 3.03$, $P < 0.05$). Whereas $CB1^{+/+}$ mice showed a decrease in freezing behaviour until day 11 ($F_{3,27} = 3.73$, $P < 0.05$), $CB1^{-/-}$ mice failed to extinguish the freezing response ($F_{3,15} = 1.03$, $P = 0.404$). A more detailed analysis of the freezing response in 20-s intervals confirmed the difference in extinction (genotype × 20-s bin interaction: $F_{11,154} = 2.60$, $P < 0.005$; Supplementary Information). These differences were due to altered short-term and long-term extinction in $CB1^{-/-}$ mice but not to increased spontaneous recovery of the freezing response (genotype: $F_{1,14} = 0.18$, $P = 0.675$; genotype × day interaction: $F_{2,28} = 1.61$, $P = 0.217$; Supplementary Information).

We next analysed whether the differences in memory extinction between the two genotypes could be attributed to alterations in sensory-motor abilities of $CB1^{-/-}$ mice, as cannabinoids are known to influence pain perception, emotionality and locomotion[4,11,12]. However, mice of either genotype showed the same pain sensitivity to a rising electric foot-shock defined as the shock intensity at which mice showed first signs of discomfort, that is, jumping and/or vocalization (Fig. 1c). Moreover, if the same animals were repeatedly exposed to the tone, there were no significant differences in freezing behaviour between the genotypes (genotype: $F_{1,12} = 1.61$, $P = 0.228$; genotype × day interaction: $F_{3,36} = 0.225$, $P = 0.878$; Fig. 1d), indicating that CB1 deficiency does not affect foot-shock-induced behavioural sensitization or unconditioned freezing to the tone. Anxiety-related behaviour was analysed on an elevated plus maze. Animals of either genotype spent the same relative time on open arms of the maze ($P > 0.05$, *t*-test and *U*-test; Fig. 1e), and made the same relative number of entries into open arms ($CB1^{+/+}$: 22.0 ± 4.0%; $CB1^{-/-}$: 21.1 ± 7.6%, $P > 0.05$, *t*-test and *U*-test). In contrast, $CB1^{-/-}$ mice showed reduced exploratory activity (number of closed-arm entries: 11.6 ± 1.1 in $CB1^{+/+}$ mice compared with 6.5 ± 1.2 in $CB1^{-/-}$ mice, $P < 0.01$, *t*-test). However, in an open-field locomotor activity test, no significant differences were found, including horizontal (Fig. 1f) and vertical locomotion, resting time, and time spent close to the walls of the box (data not shown).

The failure of $CB1^{-/-}$ mice to diminish their freezing response during a limited number of 60-s tone presentations (Fig. 1a, b) raises the question as to whether $CB1^{-/-}$ mice are able to extinguish aversive memories at all. Thus, conditioned $CB1^{-/-}$ and $CB1^{+/+}$ mice were exposed to a stronger extinction protocol (3 min tone, six exposures; Fig. 1g). Both $CB1^{+/+}$ ($F_{17,119} = 15.01$, $P < 0.000001$) and $CB1^{-/-}$ mice ($F_{17,119} = 7.59$, $P < 0.000001$) extinguished their freezing response over the course of repeated tone presentations. Nevertheless, extinction was still more pronounced in $CB1^{+/+}$ as compared with $CB1^{-/-}$ mice (genotype: $F_{1,14} = 5.30$, $P < 0.05$). Notably, the most marked differences between $CB1^{-/-}$

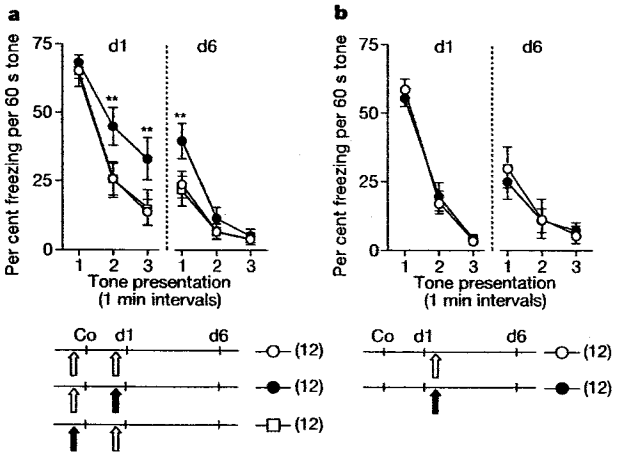

Figure 2 CB1 antagonist SR141716A impairs short-term and long-term extinction, but not acquisition and consolidation of aversive memories. **a**, Mice were treated with SR141716A (filled arrows) or vehicle (open arrows) 20 min before conditioning (Co) and the first extinction trial (d1; 3 min tone). **b**, Mice were treated with SR141716A or vehicle 10 min after the first extinction trial, as indicated. Freezing was analysed in 60-s intervals. Means ± s.e.m. are shown; number of animals are shown in parentheses. Double asterisk, $P < 0.01$ (compared with the two other groups).

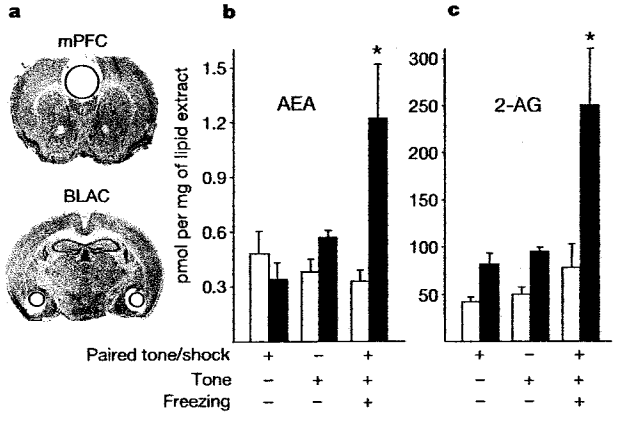

Figure 3 Re-exposure to the tone 24 h after conditioning causes increased endocannabinoid levels in the basolateral amygdala complex (BLAC) but not the medial prefrontal cortex (mPFC) of C57BL/6J mice. **a**, Micrographs of coronal brain sections showing representative examples of the dissected mPFC and BLAC. Circles indicate the size and positioning of tissue sampling. **b**, **c**, Anandamide (**b**, AEA) and 2-arachidonoylglycerol (**c**, 2-AG) levels of the three experimental groups (see text), which differed in conditioning procedure, re-exposure to the tone and resulting freezing response to the tone. Means ± s.e.m. are shown ($n = 4$ per group, 5 mice per n). Open bars, mPFC; filled bars, BLAC. Asterisk, $P < 0.05$ (compared with BLAC of the other groups).

and $CB1^{+/+}$ mice were observed during acute tone presentation (short-term extinction). Therefore, $CB1^{-/-}$ mice might be primarily impaired in short-term extinction, with a resulting impairment in long-term extinction, assessed in the course of the subsequent extinction trials. Accordingly, spontaneous recovery was not different between the genotypes (genotype: $F_{1,14} = 1.73$, $P = 0.208$; genotype × day interaction: $F_{4,56} = 1.19$, $P = 0.323$; Supplementary Information).

Our behavioural data clearly indicate an involvement of the endogenous cannabinoid system in extinction of aversive memories. However, the life-long absence of CB1 could result in developmental defects leading to the phenotype observed. It, furthermore, precludes any temporal dissection of the involvement of the endogenous cannabinoid system in different stages of memory formation. Thus, we treated wild-type C57BL/6J mice with the CB1 antagonist SR141716A (ref. 13), either before conditioning, or before the first extinction trial. Systemic application of SR141716A 20 min before the first extinction trial impaired both short-term and long-term extinction of the freezing response as compared with both vehicle-treated controls and animals treated with SR141716A before conditioning (treatment × time interaction: $F_{10,160} = 2.72$, $P < 0.005$), with no difference between the two latter treatments and with a similar performance of all three groups in the beginning of the first extinction trial (Fig. 2a). These data largely confirm the phenotype of $CB1^{-/-}$ mice (Fig. 1a, b, g), indicating that endocannabinoids have only a negligible function in memory acquisition, consolidation and recall (indicated by the similar performance at the beginning of the first extinction trial), but selectively interfere with extinction of the freezing response to the tone. Mice treated with SR141716A before the first extinction trial showed an attenuated extinction of freezing not only during the first tone presentation (short-term extinction) but also in the absence of pharmacological treatment during the first 60 s of tone presentation at day 6 (long-term extinction). Spontaneous recovery of the behavioural performance from the end of the first (day 1) to the beginning of the second tone presentation session (day 6) was not different among the three groups ($F_{2,34} = 0.29$, $P = 0.744$; Supplementary Information). Together, these findings support the idea that CB1 might be particularly important for the extinction of acute responses to the tone (short-term extinction), which, in turn, relates to behavioural extinction over repeated tone presentations (long-term extinction), without affecting spontaneous recovery of the behavioural performance. Accordingly, the CB1 antagonist had to be present at the time of tone presentation (that is, during aversive memory recall) in order to interfere with memory extinction, as SR141716A failed to affect extinction if administered immediately at the end of the extinction trial (data not shown) or 10 min later (Fig. 2b).

These observations, together with the pharmacokinetics of SR141716A (ref. 14), led us to assume that presentation of the tone during the extinction trial causes an instantaneous rise in endocannabinoid levels. To confirm this assumption, we measured in C57BL/6J mice levels of the two major endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), in brain punches of the medial prefrontal cortex (mPFC) and the basolateral amygdala complex (BLAC), both of which are thought to have central roles in extinction of aversive memories[9,15]. In those animals forming an association between tone and foot-shock, levels of AEA and 2-AG were significantly higher in the BLAC at the end of tone presentation of the extinction trial on day 1, as compared with animals with unpaired tone and foot-shock presentation on the previous day and with animals with paired tone and foot-shock presentation but no re-exposure to the tone (Fig. 3). There were no significant differences in levels of AEA and 2-AG in the mPFC, suggesting a specific involvement of endocannabinoids in extinction processes within the BLAC. Data of the two control groups indicate that both a successful tone–foot-shock association and re-exposure to the tone are required to trigger the acute increase of endocannabinoid levels.

If the endogenous cannabinoid system is activated during tone presentation, how exactly does it facilitate memory extinction? To answer this question, we performed a series of electrophysiological experiments in the BLAC of brain slices from $CB1^{-/-}$ and $CB1^{+/+}$ mice. Basic electrical properties were similar in $CB1^{-/-}$ and $CB1^{+/+}$ littermates, including input resistance and resting membrane potential (data not shown). High-frequency stimulation (HFS) in the lateral amygdala close to the external capsule induced long-term potentiation (LTP) in the basolateral amygdala of both genotypes (Fig. 4a). This effect was significantly more pronounced in $CB1^{-/-}$ than in $CB1^{+/+}$ mice (potentiation of population spike amplitude to 147 ± 11% in $CB1^{-/-}$ compared with 117 ± 8% in $CB1^{+/+}$ mice, $n = 9$, $P < 0.05$). However, we failed to affect basal synaptic transmission and LTP induction in wild-type slices superfused with SR141716A (5 μM; data not shown). This indicates that the enhanced LTP in $CB1^{-/-}$ mice might reflect long-term develop-

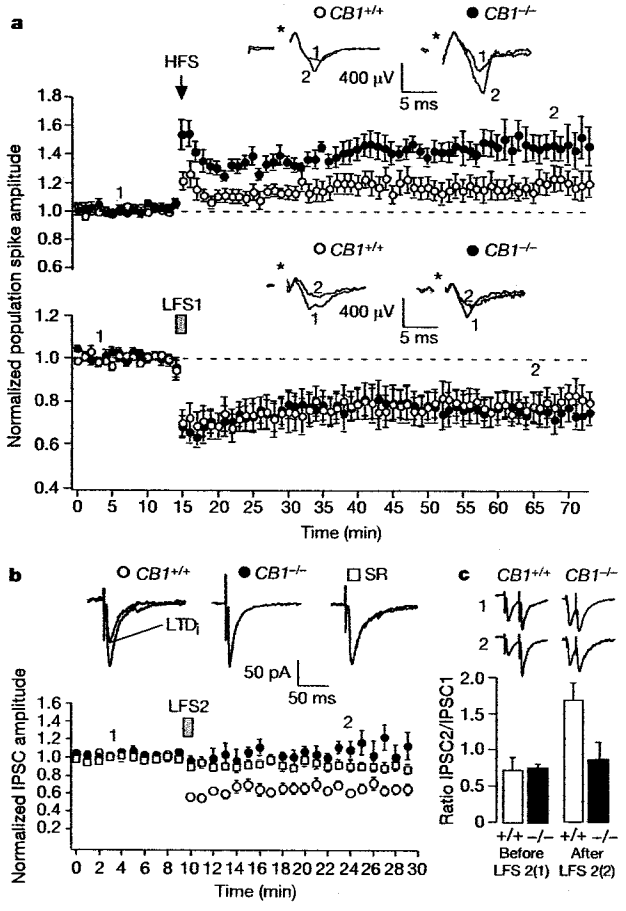

Figure 4 Endogenous cannabinoid system and synaptic plasticity in the basolateral amygdala. **a**, LTP (top) and LTD (bottom) in slices from $CB1^{+/+}$ and $CB1^{-/-}$ mice, induced by high-frequency stimulation (HFS) and low-frequency stimulation (LFS 1), respectively. Asterisks indicate stimulus artefacts. **b**, Long-term depression of IPSCs (LTD_i) requires CB1 activation. In principal neurons of slices of $CB1^{+/+}$ mice, low-frequency stimulation (LFS 2) induced a reduction of the amplitudes of isolated IPSCs. Slices of $CB1^{+/+}$ mice pre-incubated in SR141716A (SR) showed no LTD_i. LFS 2 had no effect in $CB1^{-/-}$ mice. **c**, LTD_i was accompanied by increased PPF, which was absent in $CB1^{-/-}$ mice. Insets show representative traces before and after HFS or LFS (1, 2, respectively). Means ± s.e.m. are shown.

mental adaptations to life-long absence of CB1, and cannot be easily attributed to the lack of CB1 during LTP induction. Low-frequency stimulation with 900 pulses at 1 Hz (LFS 1) of the same pathway induced a persistent decrease in excitatory synaptic transmission (long-term depression, LTD) in both $CB1^{-/-}$ and $CB1^{+/+}$ mice with no difference between genotypes (depression of population spike amplitude to 75 ± 7% in $CB1^{-/-}$ compared with 80 ± 7% in $CB1^{+/+}$ mice, $n = 9$, $P > 0.05$; Fig. 4a).

As several recent studies indicate an involvement of CB1 in GABA-mediated synaptic transmission in hippocampus[16,17] and amygdala[6], we next looked for possible differences in this process within the basolateral amygdala of $CB1^{-/-}$ and $CB1^{+/+}$ mice. Low-frequency stimulation with 100 pulses at 1 Hz (LFS 2) of the lateral amygdala close to the external capsule induced a significant suppression of isolated $GABA_A$ receptor-mediated inhibitory post-synaptic currents (IPSCs) in principal neurons of the basolateral amygdala of $CB1^{+/+}$ mice. This suppression lasted for more than 20 min (hereafter called long-term depression of IPSCs, LTD_i, to 66.7 ± 5.4%, $n = 8$, $P < 0.05$; Fig. 4b). Importantly, LTD_i was blocked in $CB1^{+/+}$ mice by SR141716A (5 μM; Fig. 4b), showing an acute involvement of the endocannabinoid system in the development of LTD_i. The involvement of CB1 in LTD_i was confirmed in $CB1^{-/-}$ mice in which LTD_i was completely abolished (to 110.1 ± 13.8%, $n = 8$, $P < 0.01$ compared with $CB1^{+/+}$; Fig. 4b). Consistent with previous reports[16,17], suppression of GABA-mediated synaptic transmission also increased paired-pulse facilitation (PPF) in $CB1^{+/+}$ ($P < 0.05$) but not in $CB1^{-/-}$ mice (Fig. 4c), indicating a local CB1-dependent decrease in GABA release from axon terminals in $CB1^{+/+}$ slices.

Extinction of aversive memories is thought to be an active mnemonic process[2]. As a new memory, it shares several attributes with other steps of memory formation[9,10,18]; however, there is increasing evidence that some cellular pathways are specifically involved in extinction, but not in acquisition or consolidation of fear memories[15,19,20]. We demonstrated a specific involvement of CB1-mediated neurotransmission in extinction of aversive memories. In principle, the enhanced excitatory synaptic plasticity in $CB1^{-/-}$ mice (LTP; Fig. 4a) might explain the prolonged maintenance of aversive memories observed in these animals (Fig. 1a, b, g). However, an enhanced LTP is expected to coincide with an increased initial freezing response in the first extinction trial[21], which was not observed in $CB1^{-/-}$ mice. Accordingly, acute blockade of CB1 by a selective antagonist failed to affect LTP induction as well as acquisition and consolidation of the aversive memory. In contrast, the same approach revealed a significant involvement of CB1 in extinction (Fig. 2a). Tone-induced recall of the aversive memory was accompanied by an activation of the endocannabinoid system within the BLAC (Fig. 3), which possibly leads to a decrease of GABA-mediated transmission in a CB1-dependent manner (LTD_i; Fig. 4b, c).

The role of GABA-mediated transmission for extinction is, however, controversial[22,23]. Within the amygdala, CB1 immunoreactivity was detected in a distinct subset of GABA-containing interneurons of the BLAC[6] (one of the sites where aversive memories might be formed and stored[24]), but not in the central nucleus of the amygdala[6] (the principal output site of the amygdala[1]). Taking into consideration that principal neurons of the BLAC and neurons of the central nucleus of the amygdala might be inversely correlated in their activities[25,26], we propose that the CB1-mediated decrease of activity of local inhibitory networks within the BLAC leads to a disinhibition of principal neurons and finally to extinction of the freezing response. The selective and locally restricted inhibition of GABA-mediated transmission might not be easily reproduced by systemic administration of GABA-interfering drugs[22,23]. Thus, future studies will have to confine such treatments to the BLAC to validate that CB1-mediated inhibition of GABA-mediated transmission is indeed crucially involved in the extinction of aversive memories mediated by CB1. It remains to be shown whether CB1 is not only involved in extinction of aversive memories but also in adaptation to aversive situations in general and/or in extinction of memories, independently from their emotional value.

Overall, our findings suggest that the endogenous cannabinoid system could represent a therapeutic target for the treatment of diseases associated with inappropriate retention of aversive memories or inadequate responses to aversive situations, such as post-traumatic stress disorders[2], phobias, and certain forms of chronic pain[11]. □

Methods

Animals

Adult male C57BL/6JOlaHsd mice (6–8 weeks; Harlan–Winkelmann) and male $CB1^{-/-}$ and $CB1^{+/+}$ littermates (10–16 weeks; see Supplementary Information) were housed individually with an inverse 12/12 h light/dark cycle (lights off at 8:00) for at least 2 weeks before starting the experiments.

Behavioural studies

Experimental procedures were approved by the Committee on Animal Health and Care of local Government. Experiments were performed between 9:00 and 14:00. Animal's behaviour was analysed in a blind fashion with regards to genotype and drug treatment. Data were analysed by analysis of variance (ANOVA) followed by Fisher's least significant difference test for planned comparisons, Mann-Whitney *U*-test or unpaired Student's *t*-test. A *P*-value of <0.05 was considered statistically significant. Experimental procedures for pain threshold and unconditioned freezing, elevated plus maze and open field are described in Supplementary Information.

Fear conditioning

For conditioning, animals were placed into conditioning chambers (MED Associates). After 3 min, a 20-s tone (9 kHz, 80 dB) was presented that co-terminated with a 2-s electric foot-shock (0.7 mA). In pharmacological experiments animals received a 1-s shock to avoid ceiling effects in the freezing response due to the combination of foot-shock and injection stress. Animals were returned to their home cages 60 s after shock application. At the given time points after conditioning, animals were placed into transparent plexiglas cylinders that differed from the conditioning context, and a 60-s or 180-s tone was presented 3 min later (extinction trials). Animals were returned to their home cages after another 60 s. Mice were experimentally naive except for the stronger extinction protocol, where they had been tested on the elevated plus maze 5 days before. Freezing behaviour (defined as the absence of all movements except for respiration) was quantified from videotapes by trained observers that were blind to genotype and drug treatment, and data were normalized to the respective observation periods.

Pharmacological treatment

SR141716A (NIMH Chemical Synthesis and Drug Supply Program) was dissolved in vehicle solution (1 drop of Tween-80 in 3 ml 2.5% dimethylsulphoxide in saline). SR141716A (3 mg per kg body weight) and vehicle were injected subcutaneously at 20 ml per kg body weight under light isofluran anaesthesia.

Measurement of endocannabinoids

C57BL/6JOlaHsd mice were randomly assigned to three groups ($n = 20$ each). On the conditioning day, two groups were conditioned as described before (paired). The remaining group received the foot-shock first and a 20 s tone 3 min later (unpaired). On the next day, all animals were placed into the cylinders, but only one of the paired groups and the unpaired group were exposed to a 3-min tone. Immediately after the end of the tone (or equivalent time in cylinder), animals were killed, brains were quickly removed and snap-frozen in isopentane/dry ice. mPFC and BLAC were punched from the frozen brain using a cryocut and cylindric brain punchers (Fine Science Tools, internal diameter 2.0 mm and 0.8 mm, respectively). Length of punches was approximately 1.6 mm for mPFC (start: bregma +2.8 mm[27]) and 1.2 mm for BLAC (start: bregma −1.0 mm[27]). Brain tissue of mPFC and bilateral BLAC, respectively, of 5 mice was pooled to obtain a single data point. Tissues (10–15 mg per data point) were dounce-homogenized with chloroform/methanol/Tris-HCl 50 mM, pH 7.4 (1/1/1 by volume) containing 5 pmol of octa-deuterated (d_8)-anandamide and 50 pmol of d_8-2-arachidonoylglycerol (Cayman Chemicals) as internal standards. Lipid-containing organic phase was dried down, weighed and pre-purified by open-bed chromatography on silica gel, and analysed by liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry (LC-APCI-MS) using a Shimadzu high-performance liquid chromatography (HPLC) apparatus (LC-10ADVP) coupled to a Shimadzu quadrupole mass spectrometer (LCMS-2010) via a Shimadzu APCI interface. Mass spectrometry analyses were carried out in the selected ion-monitoring (SIM) mode as described previously[28]. Temperature of the APCI source was 400 °C; HPLC column was a Phenomenex (5 μm, 150 × 4.5 mm) reverse phase column, eluted as described[28]. Anandamide (retention time of 14.5 min) and 2-AG (retention time of 17.0 min) quasi-molecular ions were quantified by isotope dilution with the above-mentioned deuterated standards[28] and their amounts in pmols normalized per mg of lipid extract. Data were statistically evaluated by ANOVA.

Electrophysiology

Brain slices were prepared essentially as described[29]. IPSCs and population spikes were evoked by square pulse stimuli (0.066 Hz, 5–12 mA, 200 μs) delivered by means of bipolar tungsten electrodes positioned within the lateral amygdala close to the external capsule. Population spikes were recorded in the basolateral amygdala close to lateral amygdala using glass microelectrodes (2–3 MΩ) filled with artificial cerebrospinal fluid (ACSF)[29]. HFS (five trains at 100 Hz for 1 s, 10-s interstimulus interval) was applied to induce LTP, and LFS1 (900 pulses at 1 Hz) was applied to induce LTD. Whole-cell GABA-mediated currents were isolated by adding NBQX (0.005 mM) and D-(-)-2-amino-5-phosphopentanoic acid (AP5; 0.05 mM) to ACSF (bubbled with 95% O_2/5% CO_2; pH 7.3), and were recorded from visually identified somata of principal neurons of the basolateral amygdala[30] by glass electrodes (4.5–5 MΩ)[16] containing (in mM): Mg-ATP 2, $CsCH_3SO_3$ 100, CsCl 60, EGTA 0.2, HEPES 10, $MgCl_2$ 1, QX314 5 and Na_3GTP 0.3 (pH 7.3). Patch clamp experiments were performed at 24 ± 1 °C at a holding potential of −70 mV. LTD_1 was induced by 100 stimuli at 1 Hz (LFS 2). PPF was induced as described[30]. Data are expressed as means ± s.e.m. We tested significance using the Student's *t*-test.

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Competing interests statement

The authors declare that they have no competing financial interests.

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A transcription factor response element for gene expression during circadian night

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Mammalian circadian clocks consist of complex integrated feedback loops[1–10] that cannot be elucidated without comprehensive measurement of system dynamics and determination of network structures[11]. To dissect such a complicated system, we took a systems-biological approach based on genomic, molecular and cell biological techniques. We profiled suprachiasmatic nuclei and liver genome-wide expression patterns under light/dark cycles and constant darkness. We determined transcription start sites of human orthologues for newly identified cycling genes and then performed bioinformatical searches for relationships between time-of-day specific expression and transcription factor response elements around transcription start sites. Here we demonstrate the role of the Rev-ErbA/ROR response element in gene expression during circadian night, which is in phase with *Bmal1* and in antiphase to *Per2* oscillations. This role was verified using an *in vitro* validation system, in which cultured fibroblasts transiently transfected with clock-controlled reporter vectors exhibited robust circadian bioluminescence[12].

To perform comprehensive measurement of mammalian circadian gene expression, we profiled genome-wide expression patterns of central (suprachiasmatic nuclei, SCN) and peripheral (liver) clocks every four hours during light/dark cycles (LD) or constant darkness (DD) over two days. We extracted total RNA from 50 pooled SCNs and four pooled livers at each time point, prepared biotinylated complementary RNA and used an Affymetrix mouse high-density oligonucleotide probe array (GeneChip) to determine SCN and liver gene expression.

The data obtained were analysed through two statistical cosine filters, one for LD and the other for DD time courses (see

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CANNABIS: A BREED APART

Cannabis sativa L. and *Cannabis indica* Lam. are most recognized in our society as the recreational drug called marijuana. This agent has been employed medicinally throughout much of the world for a large variety of maladies. Although the herb remains a political pariah, the trend toward "medical marijuana" has recently revealed some important secrets about our internal chemistry. One key active component of cannabis is THC, tetrahydrocannabinol, which was synthesized in the laboratory by Raphael Mechoulam in the 1960s (Mechoulam and Burstein, 1973). The question remained regarding how this unusual chemical affected the mind of man. It was not until 1993 that Devane and colleagues (1992) discovered anandamide, an endogenous cannabinoid, which revealed that marijuana works by mimicry of our own natural chemical machinery. Though the herb has been demonized, the investigation of the cannabinoid neuromodulatory system has resulted in monthly revelations about normal neurochemistry and its perturbations. Therapeutic breakthroughs in the treatment of nausea and weight loss in AIDS and chemotherapy patients, new knowledge about the immune system, control of pain, prevention of brain damage from stroke and trauma, and many other benefits are imminent as a result of these discoveries.

Anandamide activity is highest in the hippocampus, parahippocampal cortex, thalamus, striatum, and cerebellum, suggesting, among other activities, that cannabis may modulate motor, memory, and cognitive functions (Consroe, 1998).

It has also been shown that endogenous cannabinoids and their inactive metabolites combine to enhance biochemical activities' responses (the "entourage effect") (Mechoulam and Ben-Shabat, 1999). Considering the possible contributions of other cannabis components, such as flavonoids and essential oils, to therapeutic effects on mood (reviewed in McPartland and Pruitt, 1999), one must readily assent to the following observation (Mechoulam and Ben-Shabat, 1999, p. 136):

> This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them.

The fact is that we owe these advances in basic psychopharmacology to a plant, without which the understanding of a major biochemical system that is crucial to our well-being would have eluded our grasp for a much longer period of time.

Although cannabis represents a departure from the format of examination of commercially available therapeutic psychotropic herbs, the author feels that a reexamination of its potential benefits is warranted. Furthermore, a liberalization of legislation on medical cannabis use is occurring in many countries, if most slowly in the United States. Although this discussion will necessarily be truncated, the interested reader is referred to upcoming analyses in the *Journal of Cannabis Therapeutics* (Russo, 2000). Those concerned with the dangers of cannabis usage may be reassured by the book *Marijuana Myths, Marijuana Facts* (Zimmer and Morgan, 1997) and the Institute of Medicine Report (Joy, Watson, and Benson, 1999), as well as a recent article examining cognitive function in long-term cannabis smokers (Lyketsos et al., 1999).

Let us examine the history of this most controversial agent. The first records of medicinal use of cannabis may occur in the *Pên-tsao Ching*, the Chinese herbal based on the oral traditions passed down from Emperor Shên-nung in the third millennium B.C.E., written down in the first or second centuries. It was noted that the plant fruits "if taken in excess will produce hallucinations (literally 'seeing devils')" (Li, 1974, p. 446).

The *Atharva Veda* (passage 11, 6, 15), dated to between 2000 to 1400 B.C.E., provides the first mention of cannabis as a psychotropic herb under the name *bhanga*, according to G. A. Grierson (Indian Hemp Drugs Commission, 1893-1894, Appendix 3, p. 246):

> We tell of the five kingdoms of herbs headed by Soma; may it and *kuca* grass, and *bhanga* and barley, and the herb *saha* release us from anxiety.

Use of cannabis in ancient Assyria has been claimed in numerous sources. Most notably, Campbell Thompson (Thompson, 1924, 1949) documented twenty-nine citations of cannabis in ancient Assyrian medical texts of Sumerian and Akkadian vintage (early second millennium B.C.E.), as well as psychogenic effects by various methods, including fumigation. Thompson stated (1924, p. 101):

> The evidence thus indicates a plant prescribed in AM [Assyrian manuscripts] in very small doses, used in spinning and rope-making, and at the same time a drug used to dispel depression of spirits. Obviously, it is none other than hemp, *Cannabis sativa,* L.

Campbell asserted cannabis to be "an intoxicant and drug for mental exhilaration."

Herodotus, the Greek historian (circa 450 B.C.E.), documented a funeral rite of the Scythian people. They erected tents, heated stones, and placed cannabis seeds or the flowering tops upon them to produce smoke (Herodotus, 1954, p. 95):

> for when they have parties and sit round a fire, they throw some of it into the flames, and as it burns it smokes like incense, and the smell of it makes them drunk just as wine does us; and they get more and more intoxicated as more fruit is thrown on, until they jump up and start dancing and singing.

This passage lends credence to cannabis's reputation as an "assuager of grief."

Jābir ibn Hayyān in the *Kitab al-Sumum* in the eighth century also cited the psychoactive effects of cannabis (Lewis et al., 1971).

Cannabis also figured in the medical writings of Avicenna (ibn Sīnā) in the tenth century, wherein the inebriating effects of the plant leaves were noted (Ainslie, 1826), as they were, too, in the works of Maimonides (Moses ben Maimon) in the twelfth century (Meyerhof, 1940).

Leclerc documented various Arab authors' experiences with cannabis, for example, he quoted Ed-Dimachky (Leclerc, 1881, p. 118), who stated that cannabis "purifies the brain if one injects its decoction in the nose" (translation E. B. R.).

Cannabis was not without controversy in the early Islamic world and has been vilified by many contemporary authors, some even claiming that it actually provoked melancholy (Lozano Camara and Instituto de Cooperación con el Mundo Arabe, 1990).

Europeans were reminded of the psychoactivity of cannabis by Garcia da Orta (1913), a Spanish Jew who explored India in the sixteenth century. The author documented sedative and appetite-stimulating properties in his 1563 book.

In Indonesia, then known as the Dutch East Indies, Georg Everard Rumpf studied the flora, writing (Rumpf and Beekman, 1981, p. 194):

> The Indians [loose term for peoples of the East] deem this Fool's-Herb to be their *Nepenthes* which serves to drive away sorrow and bring them jollity.

Robert Burton (1907) did not neglect the therapeutic benefits of cannabis ("bange") in his encyclopedic *Anatomy of Melancholy* of 1621: "Bange is like in its effects to opium, causing a kind of ecstasy, an inclination gently to laugh" (p. 593).

In 1712, Engelbert Kaempfer published his *Amoenitatum Exoticarum Politico-Physico-Medicarum,* in which he described the psychotropic nature of cannabis as utilized in Persia and India (Dolan, 1971; Kaempfer, 1996).

In 1839, the medical use of cannabis, or Indian hemp, was reintroduced to the West from India (O'Shaughnessy, 1838-1840). He examined the effects of cannabis extract in treatment of a variety of desperate medical cases. Recoveries were documented in cases of delirium tremens (alcohol withdrawal) and tetanus. Even in rabies, which remains virtually universally fatal to this day, patients were able to attain rest, comfort, and, in terminal events, an easier passage.

In England, Clendinning (1843) used a tincture of Indian hemp to advantage in a variety of illnesses, even in cases of morphine withdrawal symptoms:

> I have no hesitation in affirming that in my hand its exhibition has usually, and with remarkably few substantial exceptions, been followed by manifest effects as a soporific or hypnotic in conciliating sleep; as an anodyne in lulling irritation; as an

> antispasmodic in checking cough and cramp; and as a nervine stimulant in removing languor and anxiety, and raising the pulse and spirits; and that these effects have been observed in both acute and chronic affections, in young and old, male and female. (p. 209)

The French physician Jacques-Joseph Moreau de Tours was the first to systematically examine the role of cannabis in psychiatric practice in his 1845 book *Du Hachisch et de l'Alientation Mentale: Études Psychologiques.* Moreau (1973) mused about its applications:

> One of the effects of hashish that struck me most forcefully and which generally gets the most attention is that manic excitement always accompanied by a feeling of gaiety and joy inconceivable to those who have never experienced it. I saw in it a mean of effectively combatting the fixed ideas of depressives, disrupting the chain of their ideas, of unfocusing their attention on such and such a subject. (p. 211)

He went on to report that initial trials had mixed results.

Subsequently, some years later, Moreau (1857) reported in detail the case study of a young man with intractable lypemania, a sort of obsessive melancholia, and its remarkable cure with cannabis. Could the same result have occurred spontaneously? Perhaps, but subsequent evidence supports a rational basis for its efficacy.

Many judged Moreau's efforts to be an ultimate failure, but not all. In 1926, Professor E. Perrot of the *Faculté de Pharmacie de Paris* stated:

> The Indian hemp, to take but one example, quite cheated the hopes of Moreau de Tours, but it would be imprudent to affirm that it will not be better utilized by the psychiatry of tomorrow! (Rouhier, 1975, p. IX) (translation E. B. R.)

In 1853, François Allemand, a French physician, wrote a utopian treatise, *Le hachych,* which was published in Paris. In it, a fictional Dr. Lebon speaks of hashish's psychotropic effects, when asked about its benefits:

> What pleasure? Without hashish, I should have died of melancholy a hundred times. . . .
>
> The most constant and remarkable property of hashish is to exalt the dominant ideas of the person who has taken it, to make him see in the clearest way his most complicated plan come to fruition without difficulty, his dearest project realized without obstacle, to furnish him with the precise intuition he seeks. Finally, it lets him taste in thought the absolute possession of everything according to his wishes, and habitual passions, and according to the direction of his thoughts at the moment the hashish acts on him. (Kimmens, 1977, pp. 117-118)

A physician in Ohio reported a notable therapeutic success with cannabis in the treatment of "hysterical insanity," a case that we would currently recognize as bipolar disease (manic depression) (McMeens, 1860). Concluding an extensive review of cannabis therapeutics, the author stated:

> In those mixed and indefinable paroxysms of an hysterical nature, I have found no remedy to control or curtail them with equal promptness and permanency. . . . In sleeplessness, where opium is contraindicated, it is an excellent substitute. . . . As a calmative and hypnotic, in all forms of nervous inquietude and cerebral excitement, it will be found an invaluable agent, as it produces none of those functional derangement or sequences that render many of the more customary remedies objectionable. (McMeens, 1860, p. 95)

John Russell Reynolds, who was to become personal physician to Queen Victoria, initially reported on various successes with an extract of cannabis in depression, lassitude, and senile restlessness (Reynolds, 1868).

In 1870, a Professor Polli of Milan documented at length another fascinating case of a young widow with an advanced melancholia with obsessional features and anxiety. She was successfully treated over ten days with *dawamesk,* an Egyptian confection composed of hashish (Polli, 1870, p. 99):

> with a steady and progressive amelioration of all the phenomena; the nights became tranquil, the intelligence just, the affec-

> tions natural. There only remained for a few days a little loquacity, some inclination to laugh unnecessarily, and a slight muscular feebleness.
>
> Some months afterwards this lady was perfectly well, lively, and in flourishing health. The cure was permanent.

Indian hemp proved to be a useful agent in treatment of delirium tremens (alcohol withdrawal) and for treating opiate addiction. One author, citing his experience and that of his colleagues, stated, "the effect was marvellous" (Tyrell, 1867, p. 244).

Referring to *Cannabis indica,* it was said (Strange, 1883, p. 14):

> in cases of melancholia, and, indeed, in all cases of mental depression with sleeplessness, I have found a valuable and almost certain ally in this drug.

By 1890, Reynolds had employed cannabis medicinally for almost forty years. As a treatment for senile insomnia, he wrote, "in this class of cases, I have found nothing comparable in utility to a moderate dose of hemp" (Reynolds, 1890, pp. 637-638). He related its effectiveness over long periods of time without resort to escalating dosages.

The same year, the treatment of delirium tremens was described (Aulde, 1890, p. 526):

> In all probability the first dose will be sufficient to arrest the vomiting, and, if the drug is pushed, the patient will gradually fall in to a natural-like sleep, and awake several hours after greatly refreshed and entirely free from the threatening symptoms presented a few hours previously.

Suckling reported successes with Indian hemp in the treatment of mania and melancholia, in quaint prose that would raise eyebrows nowadays for its misogyny:

> almost a specific in that form of insanity peculiar to women, caused by mental worry or moral shock. (1891, p. 12)

Mattison (1891) reviewed cannabis therapy in detail. One indication he advocated was treatment of addiction to cocaine, chloral hydrate, and opiates. He stated, "In these, often, it has proved an efficient substitute for the poppy." He concluded with a flourish:

> Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence.
>
> My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic. (p. 271)

At the turn of the twentieth century, a British pharmacologist touted smoking cannabis (Dixon, 1899, p. 1356):

> In cases where an immediate effect is desired the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, and exhaustion a few inhalations produce an almost immediate effect, the sense of depression, headache, feeling of fatigue disappear and the subject is enabled to continue his work, feeling refreshed and soothed.

An interesting description of cannabis intoxication provided by Lewis in 1900 is telling in its potential for therapeutic effects:

> A feeling of joyful anticipation of some unknown yet great pleasure is experienced, and there seems to be an end of all trouble and care. Without taking cognizance of the fact, past events and details grow very unimportant and the most pressing obligations are forgotten. The mind seems wholly taken up with the thoughts of the moment. Very frequently a great inexplicable sense of relief is felt, the sensation many times being identical with that experienced by one who suddenly awakes from a horrible dream to the feeling of gratitude which is always felt at its unreality. (p. 247)

Although cannabis use was essentially outlawed in the United States in the late 1930s, it has remained an agent of ethnobotanical importance around the world. In a treatise titled *Indigenous Drugs of India,* Chopra and Chopra (1957, p. 91) stated, "cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness."

In another book about medicinal plants of the subcontinent, the author asserted (Dastur, 1962, p. 67):

> Charas is the resinous exudation that collects on the leaves and flowering tops of plants [equivalent to the Arabic *hashish*]; it is the active principle of hemp; it is a valuable narcotic, especially in cases where opium cannot be administered; it is of great value in malarial and periodical headaches, migraine, acute mania, whooping cough, cough of phthisis, asthma, anaemia of brain, nervous vomiting, tetanus, convulsion, insanity, delirium, dysuria, and nervous exhaustion.

Similarly, cannabis retains many uses in the folk medicine of Southeast Asia, including smoking and ingestion as a tonic for chronic illness, after childbirth, as a soporific, and as a relaxant (Martin, 1975). In Vietnam, a use of cannabis seed was observed: "The preparation *(sac thuoc)* is used to combat loss of memory and mental confusion" (Martin, 1975, p. 172).

Despite cannabis prohibition in most countries, investigation has continued in modern times to some degree. In 1944, the LaGuardia Commission published an in-depth examination of marijuana and found its dangers vastly overstated. Therapeutic applications were even advanced (Mayor's Committee on Marihuana, 1944, p. 147): "the typical euphoria-producing action . . . might be applicable in the treatment of various types of mental depression."

As part of the study (Mayor's Committee on Marihuana, 1944), fifty-six inmates with morphine or heroin addiction were examined. A group treated with THC (tetrahydrocannabinol, the main psychoactive cannabinoid)

> had less severe withdrawal symptoms and left the hospital at the end of the treatment period in better condition than those who received no treatment or who were treated with Magendie's solution. The ones in the former group maintained their appetite and in some cases actually gained weight during the withdrawal period. (p. 147)

Efforts continue in a similar vein to treat withdrawal with cannabis and have been spearheaded by Tod Mikuriya, who has reported

on a successful use of cannabis in the treatment of alcoholism (Mikuriya, 1970). Current governmental constraints in the United States have recently rendered formal clinical studies with cannabis an extreme rarity.

A clinical study in 1976 revealed statistically significant results (Regelson et al., 1976, p. 775):

> Delta-9-THC in cancer patients at acceptable dosage (0.1 mg/kg tid, orally) had the effect of a tranquilizer and mild mood elevator, clearly without untoward effects on cognitive functioning and apparently without untoward effect on personality or emotional stability—at least as can be measured by psychological tests.

Thousands of cancer survivors have anecdotally supported similar personal observations.

Cannabis use has often been cited as an implicated etiological or aggravating factor in the development of psychosis (schizophrenia). A recent study found otherwise (Warner et al., 1994). Among the findings, psychotic patients who used marijuana had lower hospitalization rates than those who abused other substances, and they had lower rates of activation symptoms. Patients reported beneficial effects on depression, anxiety, insomnia, and pain.

Cannabis may improve night vision, according to reported observations of night fishermen in Jamaica, as reported in the journal *Nature* (West, 1991). This proposition could be scientifically verified by the use of ERG (electroretinography) testing in volunteers.

Any pharmacological discussion of cannabis is complicated by the fact that, as with any herb, it is subject to quality control issues. Cannabis is a mixture of myriad cannabinoids and essential oils that may contribute to its physiological effects. In addition, ratios of tetrahydrocannabinol (THC) and cannabidiol (CBD) are critical in observed medicinal activity. THC is primarily responsible for euphoric effects but may aggravate anxiety. CBD, in contrast, is less psychoactive, more sedative, and ameliorates anxiety. It also serves to modulate the "high" produced by THC. These relationships between cannabis components have been extensively studied in Brazil by Zuardi and colleagues (Zuardi et al., 1981, 1982, 1993, 1995; Zuardi, Guimaraes, and Moreira, 1993; Zuardi and Karniol, 1983;

Zuardi, Rodrigues, and Cunha, 1991). Although these results are not easily summarized, and the interested reader is urged to examine the source material, a good review of CBD activity is available (Zuardi and Guimaraes, 1997).

CBD had a significant effect on anxiety in normal subjects in an experimental protocol, and without significant sedation (Zuardi, Guimaraes, and Moreira, 1993).

CBD also improved symptoms of psychosis in one patient, without induction of parkinsonian symptoms, as commonly occurs with standard antipsychotic agents. Improvement did not occur with addition of haloperidol to CBD (Zuardi et al., 1995).

Dr. Lester Grinspoon, a psychiatrist at Harvard University, has pioneered and spearheaded the medical use of marijuana. His writings have frequently included personal case studies of patients whose psychiatric illnesses have been successfully treated through cannabis use (Grinspoon and Bakalar, 1997). Although critics have derided testimonials of this type as anecdotal, many of the patients failed miserably on standard pharmaceuticals but successfully alleviated their symptomatology with cannabis. How much scientific verification do the patients themselves require?

Many of these accounts document the manner in which patients were relieved on cannabis, worse without it, and helped once more upon its resumption. This represents an "N-of-1 trial" (patient acts as own control and notes effects on and off the drug) that has been widely accepted as a valid research technique in pharmacological study of conditions that are extremely rare, or in which true double blinding is impossible, as is clearly the case for cannabis.

Dr. Grinspoon recently published another series of case studies of cannabis in the treatment of bipolar disease (manic depression) (Grinspoon and Bakalar, 1998). This author believes that these accounts are extremely compelling in supporting efficacy for cannabis in this most difficult clinical problem.

Consroe (1998) has nicely reviewed the topic of brain cannabinoids in neurological disease and points out that the effect of cannabis to impair short-term memory suggests the potential utility of cannabinoid *antagonists* in treatment of dementia. Interestingly, and contrary to logic, recent reports indicate that dronabinol (synthetic THC) actually decreased the severity of disturbed behavior in

a dozen patients with Alzheimer's disease (Volicer et al., 1997). Cohen-Mansfield Agitation Inventory scores, expressed as a percentage of baseline, were diminished significantly ($p = 0.05$), while negative affect in the dronabinol group also decreased over placebo ($p = 0.004$). Dronabinol also produced weight gain in these previously anorexic subjects ($p = 0.006$). The results were sufficiently compelling to cause the drug's manufacturer to seek out a formal indication for its use in Alzheimer's disease from the FDA.

Finally, cannabis has been reported as effective in treatment of Tourette's syndrome (TS) (Hemming and Yellowlees, 1993; Moss et al., 1989; Müller-Vahl, Kolbe, and Dengler, 1997; Müller-Vahl et al., 1998, 1999; Sandyk and Awerbuch, 1988). This entity consists of a combination of involuntary movements, or tics, and pervasive features of obsessive-compulsive disorder (OCD). Cannabinoid receptors are heavily represented in the basal ganglia (Herkenham et al., 1990; Herkenham, 1993), and it has been hypothesized that this is the pathologically impaired site in TS patients.

Efficacy has been demonstrated anecdotally (Müller-Vahl et al., 1998) with cannabis in 82 percent of surveyed TS patients on both tics and OCD symptoms. The same was confirmed experimentally in one patient with dronabinol (Müller-Vahl et al., 1999). A few patients of this book's author report similar findings.

Such results have important implications. OCD represents one of the most recalcitrant disorders in psychiatry. Before 1980, no standard pharmaceuticals were significantly effective in its treatment. Nowadays, high, and sometimes massive, doses of clomipramine (a TCA) or SSRIs (Prozac and others) are required for its control.

Whereas a disorder of serotonin expression has been implicated as etiological in OCD, the necessity of these massive doses undermines that theory and, rather, supports the prospect that the current therapeutic drugs are producing secondary effects in another neurotransmitter system. What if OCD actually represents a disorder of the cannabinoid neurotransmitter system? After all, depression may be due to serotonin or norepinephrine deficiency, anxiety to GABA abnormalities, dementia to acetylcholine deficiency, and schizophrenia to dopamine excess. Conceivably, OCD and other illnesses (e.g., migraine and idiopathic bowel disease) may eventually be tied to a clinical cannabinoid deficiency state.

OCD is marked by an insurmountable preoccupation with fixed ideas (e.g., if I walk on the lawn, I will step on worms and something very bad will happen), no matter how preposterous, that withstand the patient's best efforts to submerge them through the application of logic. Cannabis, as no other substance yet discovered, allows a person to forget, and to laugh, even at one's own obsessions and compulsions. For OCD, it sounds like just what the doctor ordered.

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CHAPTER 15

Marihuana: Clinical Aspects

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The present generation of young people cannot remember when marihuana was an exotic weed with an aura of mythical power and mysterious danger. Although still illegal, it has become a commonplace part of the American social scene, used regularly by millions and occasionally used by millions more. A realistic view of this drug is now both more important and easier to achieve.

The use of marihuana reached a high point in the late 1970s and early 1980s, declined until the early 1990s, than began to rise slightly. In a 1978 National Institute on Drug Abuse (NIDA) survey, 37% of high school seniors said that they had smoked marihuana in the past 30 days. In 1989, that number fell to 17%, but by 2001, it had risen again to 22% (1). Trends at ages 18 to 25 years are similar. In 1969, 20% of high school seniors had used marihuana at least once; in 1979, 60% had; in 1989, 44%; and in 1994, 38%. Use in the past year reached a low of 22% in 1992 and rose to 30% in 1994. The perceived risk of regular marihuana use has also fallen slightly. In 1978, 35% of high school seniors said it was very risky; in 1986, 71%; in 1992, nearly 80%; in 1994, closer to 60%; and in 2001 it was 53% (2).

HISTORY

The earliest record of human *cannabis* use is a description of the drug in a Chinese compendium of medicines, the *Herbal of Emperor Shen Nung*, dated 2737 B.C. according to some sources, and 400 to 500 B.C. according to others. Marihuana was a subject of controversy even in ancient times. Some warned that the hemp plant lined the road to Hades, whereas others thought it led to paradise. Its intoxicating properties were known in Europe during the nineteenth century, and for a much longer time in South and Central America; thousands of tons of Indian hemp (the common name of the *Cannabis sativa* plant from which the drug is obtained) were produced for its commercially useful long bast fiber beginning in Jamestown, Virginia, in 1611. Nevertheless, during the early American history of *cannabis*, nothing was known of its intoxicating properties.

In 1857, Fitz Hugh Ludlow (3), largely influenced by those members of the French romantic literary movement who belonged to *Le Club des Haschischins,* published *The Hasheesh Eater: Being Passages from the Life of a Pythagorean* and made a number of American literati aware of *cannabis'* euphoriant properties. Unlike his European counterparts, Ludlow did not use hashish but, rather, Tilden's Solution, one of a number of proprietary preparations of *Cannabis indica* (an alcoholic extract of *cannabis*), which he could obtain from his local apothecary. Ludlow established a link in the public mind, albeit a very narrow segment of it, between *cannabis* the medicine and *cannabis* the intoxicating drug. However, in the half-century from the publication of his book to the appearance, across the southern border, of what we now commonly call marihuana, grass, pot, or dope (all names for the dried and chopped flowering pistillate and staminate tops and leaves of the hemp plant), even this limited awareness all but completely vanished.

In any case, throughout history the principal interest in the hemp plant has been in its properties as an agent for achieving euphoria. In this country, it is almost invariably smoked, usually as a cigarette called a "joint" or "doobie"—but elsewhere the drug is often taken in the form of a drink or in foods such as candy. Recently, a new technology of *cannabis* vaporization was developed (4–6) that exploits the property that most of the plant's physiologically active constituents boil at a temperature below that at which the material burns (7). Thus, it becomes practical to administer *cannabis* vapor via the pulmonary route without throat or lung irritation or exposure to potential carcinogens from smoke.

Drug preparations from the hemp plant vary widely in quality and potency, depending on the type (there are possibly three species or, alternatively, various ecotypes of a single species), climate, soil, cultivation, and method of preparation. When the cultivated plant is fully ripe, a sticky, golden yellow resin with a minty fragrance covers its flower clusters and top leaves. The plant's resin contains the active substances, cannabinoids and essential oil terpenoids, which are produced by the plant in glandular trichomes (7). Preparations of the drug come in three grades, identified by Indian names. The cheapest and least potent, called *bhang,* is derived from the cut tops of uncultivated plants and has a low resin content. Much of the marihuana smoked in the United States, particularly a

few years ago, was of this grade. *Ganja* is obtained from the unfertilized flowering tops and leaves of carefully selected, cultivated plants, and it has a higher quality and quantity of resin. The third and highest grade of the drug, called *charas* in India, is largely made from the resin itself, obtained from the tops of mature plants; only this version of the drug is properly called hashish. Hashish can also be smoked, eaten, or drunk. Recently, more potent and more expensive marihuana from Thailand, Hawaii, British Columbia, and California has become available in the United States. Some California growers have successfully cultivated an unpollinated plant by the early weeding out of male plants; the product is the much sought-after *sinsemilla.* Such new breeding and cultivation techniques have raised the tetrahydrocannabinol content of marihuana smoked in the United States over the last 20 years; although there are some extravagant claims made about the size of this increment, most authorities believe it has been modest (8,9). On average, street *cannabis* is not much more potent than it was in the 1960s.

The chemistry of the *cannabis* drugs is extremely complex and not completely understood. In the 1940s, it was determined that the active constituents are various isomers of tetrahydrocannabinol. The delta-9 form (hereafter called THC) has been synthesized and is believed to be the primary active component of marihuana. However, the drug's effects probably involve other components, such as cannabidiol, other cannabinoids, and terpenoids (7), and also depend on the form in which it is taken. There are more than 60 cannabinoids in marihuana and a number of them are thought to be biologically active. This activity is apparently mediated by the recently discovered receptors in the brain and elsewhere in the body that are stimulated by THC (10). This exciting discovery implied that the body produces its own version of cannabinoids for one or more useful purposes. The first of these cannabinoid-like neurotransmitters was identified in 1992 and named anandamide (*ananda* is the Sanskrit word for bliss) (11). Cannabinoid receptor sites occur not only in the lower brain but also in the cerebral cortex and the hippocampus.

The psychic effects of the drug have been described in a very extensive literature. Hashish long ago acquired a lurid reputation through the writings of literary figures, notably the group of French writers—Baudelaire, Gautier, Dumas père, and others—who formed *Le Club des Haschischins* in Paris in the 1840s. Their reports, written under the influence of large amounts of hashish, must be largely discounted as exaggerations that do not apply to moderate use of the drug. There is a story that hashish was responsible for Baudelaire's psychosis and death; the story overlooks the fact that he had relatively little experience with hashish, was in all probability actually writing about his experience with laudanum, and, moreover, had been an alcoholic and suffered from tertiary syphilis.

Bayard Taylor—the American writer, lecturer, and traveler best known for his translation of Goethe's *Faust*—wrote one of the first accounts of a *cannabis* experience in terms that began to approach a clinical description. He tried the drug in a spirit of inquiry during a visit to Egypt in 1854. His narrative of the effects follows (12):

> The sensations it then produced were... physically of exquisite lightness and airiness—mentally of a wonderfully keen perception of the ludicrous in the most simple and familiar objects. During the half hour in which it lasted, I was at no time so far under its control that I could not, with the clearest perception, study the changes through which I passed. I noted with careful attention the fine sensations which spread throughout the whole tissue of my nervous fibers, each thrill helping to divest my frame of its earthly and material nature, till my substance appeared to me no grosser than the vapors of the atmosphere, and while sitting in the calm of the Egyptian twilight I expected to be lifted up and carried away by the first breeze that should ruffle the Nile. While this process was going on, the objects by which I was surrounded assumed a strange and whimsical expression.... I was provoked into a long fit of laughter.... [The effect] died away as gradually as it came, leaving me overcome with a soft and pleasant drowsiness, from which I sank into a deep, refreshing sleep.

Perhaps a better clinical account is that of Walter Bromberg, a psychiatrist, who described the psychic effects on the basis of his own experience and many observations and talks with people while they were under the influence of marihuana (13):

> The intoxication is initiated by a period of anxiety within 10 to 30 minutes after smoking, in which the user sometimes... develops fears of death and anxieties of vague nature associated with restlessness and hyperactivity. Within a few minutes he begins to feel more calm and soon develops definite euphoria; he becomes talkative... is elated, exhilarated... begins to have... an astounding feeling of lightness of the limbs and body... laughs uncontrollably and explosively... without at times the slightest provocation... has the impression that his conversation is witty, brilliant.... The rapid flow of ideas gives the impression of brilliance of thought and observation... [but] confusion appears on trying to remember what was thought... he may begin to see visual hallucinations... flashes of light or amorphous forms of vivid color which evolve and develop into geometric figures, shapes, human faces, and pictures of great complexity.... After a longer or shorter time, lasting up to two hours, the smoker becomes drowsy, falls into a dreamless sleep and awakens with no physiologic after-effects and with a clear memory of what happened during the intoxication.

Most observers confirm Bromberg's account as a composite, somewhat exaggerated, overinclusive description of marihuana highs. They find that the effects from smoking last from 2 to 4 hours, the effects from ingestion 5 to 12 hours. For a new user, the initial anxiety that sometimes

occurs is alleviated if supportive friends are present. The intoxication heightens sensitivity to external stimuli, reveals details that would ordinarily be overlooked, makes colors seem brighter and richer, and brings out values in works of art that previously had little or no meaning to the viewer. It is as though the *cannabis*-intoxicated adult perceives the world with some of the newness, wonder, curiosity, and excitement of a child; the person's world becomes more interesting and details that had been taken for granted now attract more attention. The high also enhances the appreciation of music; many jazz and rock musicians have said that they perform better under the influence of marihuana, but this effect has not been objectively confirmed.

The sense of time is distorted: 10 minutes may seem like an hour. Curiously, there is often a splitting of consciousness, so that the smoker, while experiencing the high, is at the same time an objective observer of their own intoxication. The person may, for example, be afflicted with paranoid thoughts, yet at the same time be reasonably objective about them—laughing or scoffing at them and, in a sense, enjoying them. The ability to retain a degree of objectivity may explain why many experienced users of marihuana manage to behave in a perfectly sober fashion in public even when they are highly intoxicated.

Although the intoxication varies with psychological set and social setting, the most common response is a calm, mildly euphoric state in which time slows and sensitivity to sights, sounds, and touch is enhanced. The smoker may feel exhilaration or hilarity and notice a rapid flow of ideas with a reduction in short-term memory. Images sometimes appear before closed eyes; visual perception and body image may undergo subtle changes. It is dangerous to operate complex machinery, including automobiles, under the influence of marihuana, because it slows reaction time and impairs attention and coordination. There is uncertainty as to whether some impairment persists for several hours after the feeling of intoxication has passed (14,15).

Marihuana is sometimes referred to as a hallucinogen. Many of the phenomena associated with lysergic acid diethylamide (LSD) and LSD-type substances can be produced by *cannabis*, but only at very high dosage. As with LSD, the experience often has a wave-like aspect. Other phenomena commonly associated with both types of drugs are distorted perception of various parts of the body, spatial and temporal distortion, depersonalization, increased sensitivity to sound, synesthesia, heightened suggestibility, and a sense of thinking more clearly and having deeper awareness of the meaning of things. Anxiety and paranoid reactions are also sometimes seen as consequences of either drug. However, the agonizingly nightmarish reactions that even the experienced LSD user may endure are quite rare among experienced marihuana smokers, not simply because they are using a far less potent drug, but also because they have much closer and continuing control over the extent and type of reaction they wish to induce. Furthermore, *cannabis* has a tendency to produce sedation, whereas LSD and LSD-type drugs may induce long periods of wakefulness and even restlessness. Unlike LSD, marihuana does not dilate the pupils or materially heighten blood pressure, reflexes, and body temperature. (On the other hand, it does increase the pulse rate, while lowering blood pressure.) Tolerance develops rapidly with LSD-type drugs but little with *cannabis*. Finally, marihuana lacks the potent consciousness-altering qualities of LSD, peyote, mescaline, psilocybin, and other hallucinogens; it is questionable whether in the doses ordinarily used in this country it can produce true hallucinations. These differences, particularly the last, cast considerable doubt on marihuana's credentials for inclusion among the hallucinogens.

HEALTH EFFECTS OF MARIHUANA USE

In recent years, the psychological and physical effects of long-term use have caused most concern. Studies are often conflicting and permit various views of marihuana's possible harmfulness. This complicates the task of presenting an objective statement about the issue.

One of the first questions asked about any drug is whether it is addictive or produces dependence. This question is hard to answer because the terms *addiction* and *dependence* have no agreed-to definitions. Two recognized signs of addiction are tolerance and withdrawal symptoms; these are rarely a serious problem for marihuana users. In the early stages, they actually become more sensitive to the desired effects. After continued heavy use, some tolerance to both physiologic and psychological effects develops, although it seems to vary considerably among individuals. Almost no one reports an urgent need to increase the dose to recapture the original sensation. What is called *behavioral tolerance* may be partly a matter of learning to compensate for the effects of high doses, and may explain why farm workers in some Third World countries are able to do heavy physical labor while smoking a great deal of marihuana (16).

A mild withdrawal reaction also occurs in animal experiments and possibly in some human beings who take high doses for a long time. The rarely reported mild symptoms are anxiety, insomnia, tremors, and chills, lasting for a day or two. It is unclear how common this reaction is; in a Jamaican study, heavy ganja users did not report abstinence symptoms when withdrawn from the drug. In any case, there is little evidence that the withdrawal reaction ordinarily presents serious problems to marihuana users or causes them to go on taking the drug. In a recent comprehensive review, *cannabis* withdrawal was seen as producing symptoms that were low level to nonexistent, with inconsistent onset and offset, with heterogeneous effects claimed with greatest support for transient agitation, appetite change, and sleep disturbance (17). In sum, the concept of *cannabis* withdrawal was considered unproven.

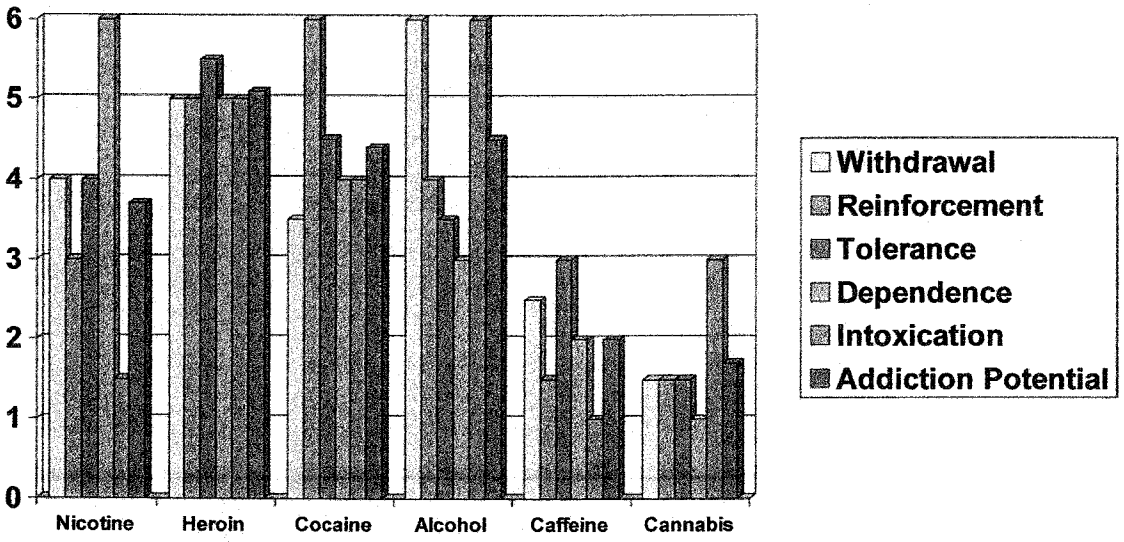

FIG. 15.1. Addiction ratings. From Henningfield, Benowitz. *New York Times* 1994 Aug 2:C3, with permission.

In a more important sense, dependence means an unhealthy and often unwanted preoccupation with a drug to the exclusion of most other things. People suffering from drug dependence find that they are constantly thinking about the drug, or intoxicated, or recovering from its effects. The habit impairs their mental and physical health and hurts their work, family life, and friendships. They often know that they are using too much and repeatedly make unsuccessful attempts to cut down or stop. These problems seem to afflict proportionately fewer marihuana smokers than users of alcohol, tobacco, heroin, or cocaine. Even heavy users in places like Jamaica and Costa Rica do not seem to be dependent in this damaging sense. Marihuana's capacity to lead to psychological dependence is not as strong as that of either tobacco or alcohol. Two experts from the University of California, San Francisco, and the National Institute on Drug Abuse independently compared the dependency potential of *cannabis*, alcohol, nicotine, caffeine, cocaine, and heroin (18,19). Cannabis was considered by both to carry the lowest overall risk (Fig. 15.1).

It is often difficult to distinguish between drug use as a cause of problems and drug use as an effect; this is especially true in the case of marihuana. Most people who develop a dependency on marihuana would also be likely to develop other dependencies because of anxiety, depression, or feelings of inadequacy. The original condition is likely to matter more than the attempt to relieve it by means of the drug. The troubled teenager who smokes *cannabis* throughout the school day certainly has a problem, and excessive use of marihuana may be one of its symptoms.

The idea has persisted that in the long run smoking marihuana causes some sort of mental or emotional deterioration. In three major studies conducted in Jamaica, Costa Rica, and Greece, researchers compared heavy long-term *cannabis* users with nonusers and found no evidence of intellectual or neurologic damage, no changes in personality, and no loss of the will to work or participate in society (20–22). The Costa Rican study showed no difference between heavy users (seven or more marihuana cigarettes a day) and lighter users (six or fewer cigarettes a day). Experiments in the United States show no effects of fairly heavy marihuana use on learning, perception or motivation over periods as long as 1 year (23–26).

On the other side are clinical reports of a personality change called the *amotivational syndrome*. Its symptoms are said to be passivity, aimlessness, apathy, uncommunicativeness, and lack of ambition. Some proposed explanations are hormone changes, brain damage, sedation, and depression. Because the amotivational syndrome does not seem to occur in Greek or Caribbean farm laborers, some writers suggest that it affects only skilled and educated people who need to do more complex thinking (21,22,27). However, there is no credible evidence that what is meant by this syndrome is related to any inherent properties of the drug rather than to different sociocultural adaptations on the part of the users.

The problem of distinguishing causes from symptoms is particularly acute here. Heavy drug users in our society are often bored, depressed, and listless, or alienated, cynical, and rebellious. Sometimes the drugs cause these states of mind, and sometimes they result from personality

characteristics that lead to drug abuse. Drug abuse can be an excuse for failure, or a form of self-medication. Because of these complications and the absence of confirmation from controlled studies, the existence of an amotivational syndrome caused by *cannabis* use has to be regarded as unproved.

Much attention has also been devoted to the idea that marihuana smoking leads to the use of opiates and other illicit drugs—the stepping stone hypothesis, now commonly referred to as the gateway hypothesis, which was rejected after extensive study by the Institute of Medicine (28) and the Canadian Senate (29). In this country, almost everyone who uses any other illicit drug has smoked marihuana first, just as almost everyone who smokes marihuana has drunk alcohol first. Anyone who uses any given drug is more likely to be interested in others, for some of the same reasons. People who use illicit drugs, in particular, are somewhat more likely to find themselves in company where other illicit drugs are available. None of this proves that using one drug leads to or causes the use of another. Most marihuana smokers do not use heroin or cocaine, just as most alcohol drinkers do not use marihuana. The metaphor of stepping stones suggests that if no one smoked marihuana it would be more difficult for anyone to develop an interest in opiates or cocaine. There is no convincing evidence for or against this. What is clear is that at many times and places marihuana has been used without these drugs, and that these drugs have been used without marihuana.

Only the unsophisticated continue to believe that *cannabis* leads to violence and crime. Indeed, instead of inciting criminal behavior, *cannabis* may tend to suppress it. The intoxication induces a mild lethargy that is not conducive to any physical activity, let alone the commission of crimes. The release of inhibitions results in fantasy and verbal (rather than behavioral) expression. During the high, marihuana users may say and think things they would not ordinarily say and think, but they generally do not do things that are foreign to their nature. If they are not already criminals, they will not commit crimes under the influence of the drug.

Does marihuana induce sexual debauchery? This popular impression may owe its origin partly to writers' fantasies and partly to the fact that users in the Middle East once laced the drug with what they thought were aphrodisiacs. In actuality, there is little evidence that *cannabis* stimulates sexual desire or power. On the other hand, there are those who contend, with equally little substantiation, that marihuana weakens sexual desire. Many marihuana users report that the high enhances the enjoyment of sexual intercourse, and it has been an aid to tantric sexual meditation in India and Tibet since ancient times (30). This appears to be true in the same sense that the enjoyment of art and music is apparently enhanced. It is questionable, however, whether the intoxication breaks down barriers to sexual activity that are not already broken.

Does marihuana lead to physical and mental degeneracy? Reports from many investigators, particularly in Egypt and parts of the Orient, indicate that long-term users of the potent versions of *cannabis* are, indeed, typically passive, nonproductive, slothful, and totally lacking in ambition. This suggests that chronic use of the drug in its stronger forms may have debilitating effects, just as prolonged heavy drinking does. There is a far more likely explanation, however. Many of those who take up *cannabis* in these countries are poverty stricken, hungry, sick, hopeless, or defeated, seeking through this inexpensive drug to soften the impact of an otherwise unbearable reality. This also applies to many of the "potheads" in the United States. In most situations one cannot be certain which came first: the drug, on the one hand, or the depression, anxiety, feelings of inadequacy, or the seemingly intolerable life situation on the other. Numerous chronic use studies have failed to differentiate personality differences between *cannabis* users and nonusers.

There is a substantial body of evidence that moderate use of marihuana does not produce physical or mental deterioration. One of the earliest and most extensive studies of this question was an investigation conducted by the British government in India in the 1890s. The investigating agency, called the Indian Hemp Drugs Commission, interviewed some 800 people—including *cannabis* users and dealers, physicians, superintendents of mental asylums, religious leaders, and a variety of other authorities—and in 1894 published a report of more than 3,000 pages. It concluded that there was no evidence that moderate use of the *cannabis* drugs produced any disease or mental or moral damage, or that it tended to lead to excess any more than did the moderate use of whiskey (31,32).

In the LaGuardia study in New York City, an examination of chronic users who had averaged about seven marihuana cigarettes a day (a comparatively high dosage) over a long period (the mean was 8 years) showed that they had suffered no demonstrable mental or physical decline as a result of their use of the drug (33). The 1972 report of the National Commission on Marihuana and Drug Abuse (34), although it did much to demythologize *cannabis*, cautioned that, of people in the United States who used marihuana, 2% became heavy users and that these abusers were at risk, but it did not make clear exactly what risk was involved. Furthermore, since the publication of this report, several controlled studies of chronic heavy use have been completed that have failed to establish any pharmacologically induced harmfulness, including personality deterioration or the development of the so-called amotivational syndrome (21–26, 35–37). The most recent government-sponsored review of *cannabis*, *Marijuana and Medicine*, conducted by the Institute of Medicine, while cautious in its summary statement, found little documentation for most of the alleged harmfulness of this substance (28).

A common assertion made about *cannabis* is that it may lead to psychosis. The literature on this subject is vast,

and it divides into all shades of opinion. Many psychiatrists in India, Egypt, Morocco, and Nigeria have declared emphatically that the drug can produce insanity; others insist that it does not. One of the authorities most often quoted in support of the indictment is Benabud of Morocco. He believes that the drug produces a specific syndrome called "*cannabis* psychosis." His description of the identifying symptoms is far from clear, however, and other investigators dispute the existence of such a psychosis. The symptoms said to characterize this syndrome are also common to other acute toxic states, including, particularly in Morocco, those associated with malnutrition and endemic infections. Benabud estimates that the number of kif (marihuana) smokers suffering from all types of psychosis is not more than 5 in 1,000 (38); this rate, however, is lower than the estimated total prevalence of all psychoses in populations of other countries. One would have to assume either (a) that there is a much lower prevalence of psychoses other than *cannabis* psychosis among kif smokers in Morocco or (b) that there is no such thing as a *cannabis* psychosis and the drug is contributing little or nothing to the prevalence rate for psychoses.

Bromberg, in a report of one of his studies, listed 31 patients whose psychoses he attributed to the toxic effects of marihuana. Of these 31, however, 7 patients were already predisposed to functional psychoses that were only precipitated by the drug, 7 others were later found to be schizophrenics, and 1 was later diagnosed as a manic-depressive (39). The Chopras in India, in examinations of 1,238 *cannabis* users, found only 13 users to be psychotic, which is about the usual prevalence of psychosis in the total population in Western countries (40). In the LaGuardia study, 9 of 77 people who were studied intensively had a history of psychosis; however, this high rate could be attributed to the fact that all those studied were patients in hospitals or institutions. Allentuck and Bowman, the psychiatrists who examined this group, concluded that "marihuana will not produce psychosis *de novo* in a well-integrated, stable person" (41).

A 1976 article by Thacore and Shukla revived the concept of the *cannabis* psychosis (42). The authors compared 25 people with what they call a paranoid psychosis precipitated by *cannabis* with an equal number of paranoid schizophrenics. The *cannabis* psychotics were described as patients in whom there had been a clear temporal relation between prolonged abuse of *cannabis* and the development of a psychosis on more than two occasions. All had used *cannabis* heavily for at least 3 years, mainly in the form of bhang, the weakest of the three preparations common in India (it is usually drunk as a tea or eaten in doughy pellets). In comparison with the schizophrenics, the *cannabis* psychotics were described as more panicky, elated, boisterous, and communicative; their behavior was said to be more often violent and bizarre, and their mental processes characterized by rapidity of thought and flight of ideas without schizophrenic thought disorder. The prognosis was said to be good; the symptoms could be easily relieved by phenothiazines and recurrence prevented by a decision not to use *cannabis* again. The syndrome was distinguished from an acute toxic reaction by the absence of clouded sensorium, confusion, and disorientation. Thacore and Shukla did not provide enough information to justify either the identification of their 25 patients' conditions as a single clinical syndrome or the asserted relation to *cannabis* use. They had little to say about the amount of *cannabis* used, except that relatives of the patients regarded it as abnormally large; they did not discuss the question of why the psychosis is associated with bhang rather than the stronger *cannabis* preparations ganja and charas. The meaning of "prolonged abuse on more than two occasions" in the case of men who were constant heavy *cannabis* users was not clarified, and the temporal relation between this situation and psychosis was not specified. Moreover, the *cannabis*-taking habits of the control group of schizophrenics were not discussed—a serious omission where use of bhang is so common. The patients described as *cannabis* psychotics were probably a heterogeneous mixture, with acute schizophrenic breaks, acute manic episodes, severe borderline conditions, and a few symptoms actually related to acute *cannabis* intoxication, mainly anxiety-panic reactions and a few psychoses of the kind that can be precipitated in unstable people by many different experiences of stress or consciousness change (42).

The explanation for such psychoses is that a person maintaining a delicate balance of ego functioning—so that, for instance, the ego is threatened by a severe loss, or a surgical assault, or even an alcoholic debauch—may also be overwhelmed or precipitated into a psychotic reaction by a drug that alters, however mildly, the person's state of consciousness. This concatenation of factors—a person whose ego is already overburdened in its attempts to manage a great deal of anxiety and to prevent distortion of perception and body image, plus the taking of a drug that, in some persons, promotes just these effects—may, indeed, be the last straw in precipitating a schizophrenic break. Of 41 first-break acute schizophrenic patients studied by Dr. Grinspoon at the Massachusetts Mental Health Center, it was possible to elicit a history of marihuana use in 6 (43). In 4 of the 6 patients, it seemed quite improbable that the drug could have had any relation to the development of the acute psychosis, because the psychosis was so remote in time from the drug experience. Careful history taking and attention to details of the drug experiences and changing mental status in the remaining two patients failed either to implicate or exonerate marihuana as a precipitant in their psychoses.

Our own clinical experience and that of others (44) suggests that *cannabis* may precipitate exacerbations in the psychotic processes of some schizophrenic patients at a time when their illnesses are otherwise reasonably well-controlled with antipsychotic drugs. In these patients, it is often difficult to determine whether the use of *cannabis* is simply a precipitant of the psychosis or whether it is

an attempt to treat symptomatically the earliest perceptions of decompensation; needless to say, the two possibilities are not mutually exclusive. There is little support for the idea that *cannabis* contributes to the etiology of schizophrenia. And in one recently reported case, a 19-year-old schizophrenic woman was more successfully treated with cannabidiol (one of the cannabinoids in marihuana) than she had been with haloperidol (Haldol) (45).

A recent study from Sweden on schizophrenia is most suspect (46). The authors examined Swedish conscripts from 1969. This investigation seems to be an attempt to rehabilitate an extremely criticized study of the same cohort published in 1987 (47), which had been thoroughly criticized (48). In the current study, the authors claim that based on their data, up to 13% of schizophrenia incidence could be attributable to *cannabis*. This is an unsubstantiated allegation, given that only 1.4% of the conscripts that ever smoked *cannabis* wound up schizophrenic. Men of such age are at the critical time in development of the disorder. All of the eventual schizophrenics in the earlier study were recognized to have some psychiatric issue before they entered the service!

Another recent study examined a cohort of young New Zealanders for *cannabis* use versus development of adult psychosis (49). In this brief article, "controls" smoked *cannabis* zero to two times, while "*cannabis* users" took the drug "three times or more" by age 15 years and continued at some unspecified rate of intake by age 18 years. Supposedly smoking *cannabis* increased the incidence of psychosis in adults, and it was more likely the earlier they began. If *cannabis* were truly etiologic in the development of psychosis, it would be reasonable to expect some dose–response effect. That is not evident here in any respect.

Interestingly, *cannabis* may ameliorate certain symptoms of psychosis (50), including activation symptoms and subjective complaints of depression, anxiety, insomnia, and pain. It is noteworthy that levels of anandamide are elevated in the brains of schizophrenics (51).

Although there is little evidence for the existence of a *cannabis* psychosis, it seems clear that the drug may precipitate in susceptible people one of several types of mental dysfunction. The most serious and disturbing of these is the toxic psychosis. This is an acute state that resembles the delirium of a high fever. It is caused by the presence in the brain of toxic substances that interfere with a variety of cerebral functions. Generally speaking, as the toxins disappear, so do the symptoms of toxic psychosis. This type of reaction may be caused by any number of substances taken either as intended or inadvertent overdoses. The syndrome often includes clouding of consciousness, restlessness, confusion, bewilderment, disorientation, dream-like thinking, apprehension, fear, illusions, and hallucinations. It generally requires a rather large ingested dose of *cannabis* to induce a toxic psychosis. Such a reaction is apparently much less likely to occur when *cannabis* is smoked, perhaps because not enough of the active substances can be absorbed sufficiently rapidly, or possibly because the process of smoking modifies in some yet unknown way those cannabinoids that are most likely to precipitate this syndrome.

Some marihuana users suffer what are usually short-lived, acute, anxiety states, sometimes with and sometimes without accompanying paranoid thoughts. The anxiety may reach such proportions as properly to be called panic. Such panic reactions, although uncommon, probably constitute the most frequent adverse reaction to the moderate use of smoked marihuana. During this reaction, the sufferer may believe that the various distortions of bodily perceptions mean that the sufferer is dying or is undergoing some great physical catastrophe, and similarly the individual may interpret the psychological distortions induced by the drug as an indication of the sufferer's loss of sanity. Panic states may, albeit rarely, be so severe as to incapacitate, usually for a relatively short period of time. The anxiety that characterizes the acute panic reaction resembles an attenuated version of the frightening parts of an LSD or other psychedelic experience—the so-called bad trip. Some proponents of the use of LSD in psychotherapy assert that the induced altered state of consciousness involves a lifting of repression. Although the occurrence of a global undermining of repression is questionable, many effects of LSD do suggest important alterations in ego defenses. These alterations presumably make new percepts and insights available to the ego; some, particularly those most directly derived from primary process, may be quite threatening, especially if there is no comfortable and supportive setting to facilitate the integration of the new awareness into the ego organization. Thus, psychedelic experiences may be accompanied by a great deal of anxiety, particularly when the drugs are taken under poor conditions of set and setting; to a much lesser extent, the same can be said of *cannabis*.

These reactions are self-limiting, and simple reassurance is the best method of treatment. Perhaps the main danger to the user is that the user will be diagnosed as having a toxic psychosis. Users with this kind of reaction may be quite distressed, but they are not psychotic. The *sine qua non* of sanity, the ability to test reality, remains intact, and the panicked user is invariably able to relate the discomfort to the drug. There is no disorientation, nor are there true hallucinations. Sometimes this panic reaction is accompanied by paranoid ideation. The user may, for example, believe that the others in the room, especially if they are not well known, have some hostile intentions, or that someone is going to inform on the user, often to the police, for smoking marihuana. Generally speaking, these paranoid ideas are not strongly held, and simple reassurance dispels them. Anxiety reactions and paranoid thoughts are much more likely in someone who is taking the drug for the first time or in an unpleasant or unfamiliar setting, than in an experienced user who is comfortable with the surroundings and companions; the reaction is very rare where marihuana is a casually accepted part of the social scene. The likelihood varies directly with

the dose and inversely with the user's experience; thus, the most vulnerable person is the inexperienced user who inadvertently (often precisely because the inexperienced user lacks familiarity with the drug) takes a large dose that produces perceptual and somatic changes for which the user is unprepared.

One rather rare reaction to *cannabis* is the flashback, or spontaneous recurrence of drug symptoms while not intoxicated. Although several reports suggest that this may occur in marihuana users even without prior use of any other drug (43), in general, it seems to arise only in those who have used more powerful hallucinogenic or psychedelic drugs. There are also some people who have flashback experiences of psychedelic drug trips while smoking marihuana; this is sometimes regarded as an extreme version of a more general heightening of the marihuana high that occurs after the use of hallucinogens. Many people find flashbacks enjoyable, but to others they are distressing. They usually fade with the passage of time. It is possible that flashbacks are attempts to deal with primary process derivatives and other unconscious material that has breached the ego defenses during the psychedelic or *cannabis* experience.

Rarely, but especially among new users of marihuana, there occurs an acute depressive reaction. It is generally rather mild and transient but may sometimes require psychiatric intervention. This type of reaction is most likely to occur in a user who has some degree of underlying depression; it is as though the drug allows the depression to be felt and experienced as such. Again, set and setting play an important part. Cannabis has been of benefit in mood stabilization in case reports from patients with bipolar disease (52).

Most recent research on the health hazards of marihuana concerns its long-term effects on the body. The main physiologic effects of *cannabis* are increased appetite, a faster heartbeat, and slight reddening of the conjunctiva. Although the increased heart rate could be a problem for people with cardiovascular disease, dangerous physical reactions to marihuana are almost unknown. No human being is known to have died of an overdose. By extrapolation from animal experiments, the ratio of lethal to effective (intoxicating) dose is estimated to be on the order of thousands to one.

Studies have examined the brain, the immune system, the reproductive system, and the lungs. Suggestions of long-term damage come almost exclusively from animal experiments and other laboratory work. Observations of marihuana users and the Caribbean, Greek, and other studies reveal little disease or organic pathology associated with the drug (21,22,27,53).

For example, there are several reports of damaged brain cells and changes in brain-wave readings in monkeys smoking marihuana, but neurologic and neuropsychological tests in Greece, Jamaica, and Costa Rica found no evidence of functional brain damage. A recent study of enrolled patients in the Compassionate Use Investigational New Drug Program in the United States also demonstrated no significant electroencephalograph (EEG) or P300 changes (54). Damage to white blood cells has also been observed in the laboratory, but again, its practical importance is unclear. Whatever temporary changes marihuana may produce in the immune system, they have not been found to increase the danger of infectious disease or cancer. If there were significant damage, we might expect to find a higher rate of these diseases among young people beginning in the 1960s, when marihuana first became popular. There is no evidence of that. Recent studies in human immunodeficiency virus (HIV) (55) and in the Missoula Chronic Use Study (54) also failed to demonstrate deleterious effects on white blood cell or CD4 counts.

The effects of marihuana on the reproductive system are a more complicated issue. In men, a single dose of THC lowers sperm count and the level of testosterone and other hormones. Tolerance to this effect apparently develops; in the Costa Rican study, marihuana smokers and controls had the same testosterone levels. Although the smokers in that study began using marihuana at an average age of 15 years, it had not affected their masculine development. There is no evidence that the changes in sperm count and testosterone produced by marihuana affect sexual performance or fertility.

In animal experiments, THC has also been reported to lower levels of female hormones and to disturb the menstrual cycle. When monkeys, rats, and mice are exposed during pregnancy to amounts of THC equivalent to a heavy human smoker's dose, stillbirths and decreased birth weight are sometimes reported in their offspring. There are also reports of low birth weight, prematurity, and even a condition resembling the fetal alcohol syndrome in some children of women who smoke marihuana heavily during pregnancy. The significance of these reports is unclear because controls are lacking and other circumstances make it hard to attribute causes. No endocrine changes were observed in the Missoula Chronic Use Study (54). To be safe, pregnant and nursing women should follow the standard conservative recommendation to avoid all drugs, including *cannabis*, that are not absolutely necessary. Nonetheless, evidence from a well-controlled study of *cannabis*-only smokers in Jamaica are supportive of a low risk to their children (56).

A well-confirmed danger of long-term, heavy marihuana use is its effect on the lungs. Smoking narrows and inflames air passages and reduces breathing capacity; damage to bronchial cells has been observed in hashish smokers. The possible side effects include bronchitis, emphysema, and lung cancer. Interestingly, one study failed to demonstrate emphysematous degeneration in *cannabis* smokers over time (57). Marihuana smoke contains the same carcinogens as tobacco smoke, usually in somewhat higher concentrations, at least in *cannabis* supplied

by NIDA. THC may actually interfere with a key biochemical step in carcinogenesis (58). Marihuana is also inhaled more deeply and held in the lungs longer, which increases the danger (59,60). On the other hand, almost no one smokes 20 marihuana cigarettes a day. Marihuana of higher potency may reduce the danger of respiratory damage, because less smoking is required for the desired effect. There is now some experimental evidence demonstrating that high-potency THC cigarettes are smoked less vigorously than those of low potency; the user takes smaller and shorter puffs, inhaling less with each puff (61). Vaporization technology may also reduce risks (62).

It is hard to generalize about abuse or define specific treatments, because the problems associated with marihuana are so vague, and cause and effect so hard to determine. Marihuana smokers may be using the drug as a facet of adolescent exploration, to demonstrate rebelliousness, to cope with anxiety, to medicate themselves for early symptoms of mental illness, or, most commonly, simply for pleasure.

The complexity of the problem is illustrated by a most important long-term study by two Berkeley psychologists (63). Shedler and Block followed the progress of 101 San Francisco children of both sexes from ages 5 to 18 years, and gave them personality tests at 7, 11, and 18 years of age. By the end of the study, 68% had used marihuana and 39% had used it once a week or more; large minorities had also used cocaine, hallucinogens, and prescription stimulants and sedatives. Three main groups could be distinguished: 29 "abstainers" who had used no illicit drugs; 36 "experimenters" who had used marihuana no more than once a month and had tried at most one other drug; and 20 "frequent users" who had smoked marihuana at least once a week and had used at least one other drug. The other 16 fit into none of these categories and were not included in the study.

Striking personality differences among the three groups appeared in childhood, long before any drug use. The frequent users, as early as age 7 years, got along poorly with other children and had few friends. They found it difficult to think ahead and lacked confidence in themselves. They were untrustworthy and seemingly indifferent to moral questions. At age 11 years they were described as inattentive, uncooperative, and vulnerable to stress. At age 18 years, they were insecure, alienated, impulsive, undependable, self-indulgent, inconsiderate, and unpredictable in their moods and behavior; they overreacted to frustration; they felt personally inadequate, as well as victimized and cheated. They had lower high school grades than adolescents in the other two groups.

Abstainers, at age 7 years, were described as inhibited, conventional, obedient, and lacking in creativity. At age 11 years they were shy, neat, and orderly, eager to please, but lacking in humor, liveliness, and expressiveness. The terms that best described them at age 18 years were tense, overcontrolled, moralistic, anxious, and lacking in social ease or personal charm. Their high school grades were average.

The happy mean, statistically, was found in the "experimenters." They were more likely to be warm, responsive, curious, open, active, and cheerful from the age of 7 years on. In the three broad categories of personal happiness, relations with others, and rational self-control, frequent users were doing worst and experimental users best. The authors pointed out that studies comparing moderate drinkers with alcoholics and abstainers have found similar personality differences.

To find some sources of these differences, the authors examined experiments conducted when the children were only 5 years old. Their parents' behavior was observed as they worked with the child on a laboratory task involving blocks and mazes. Mothers of both frequent users and abstainers tended to be cold and unresponsive. They gave their children little encouragement but insisted that they perform well; and the experience seemed unpleasant for both mother and child. Fathers of frequent users did not differ from fathers of experimenters, but abstainers' fathers were impatient, hypercritical, and domineering.

According to the authors, frequent drug users believe that they have nothing to look forward to and are therefore drawn to the immediate gratification provided by drugs. Their alienation and impulsiveness might have roots in their relationship with their mothers. The problems of abstainers are also serious, but they attract less attention, because they are less troublesome for society. Abstainers suppress their impulses to avoid feeling vulnerable, perhaps because they have internalized the attitudes of harsh, authoritarian fathers. Experimental users are the largest and most typical group. At least in the San Francisco area in the 1980s, reasonably inquisitive, open, and independent adolescents experimented with marihuana as part of growing up.

The inverted U-shaped relationship between the degree of drug use and psychological health suggests that the need for therapy would also describe such a curve. The fact that among the abstainers are to be found many individuals who could profit from psychotherapy is not relevant to this discussion of marihuana. The important question concerns the indications for therapy for those who comprise the other two arms of the curve. Given the current prevalence of drug use in our society, the developmentally appropriate propensity of adolescents to explore and experiment, and the relatively benign sequelae of such experimentation with *cannabis*, it is obvious that therapy is not properly indicated for young people who fit the description of the "experimenter."

It is appropriate to consider psychotherapy for the frequent adolescent users of marihuana. The picture that emerges is "one of a troubled adolescent who is interpersonally alienated, emotionally withdrawn, and manifestly unhappy, and who expresses his or her maladjustment through undercontrolled, overtly antisocial behavior"

(63). They are described as being "overreactive to minor frustrations, likely to think and associate to ideas in unusual ways, having brittle ego-defense systems, self-defeating, concerned about the adequacy of their bodily functioning, concerned about their adequacy as persons, prone to project their feelings and motives onto others, feeling cheated and victimized by life, and having fluctuating moods."

Obviously, psychotherapy is not inappropriate for individuals who exemplify this description. But it should be emphasized that this is not psychotherapy for marihuana abuse; it is therapy for the underlying psychopathology, one of whose symptoms is the abuse of *cannabis*. It is no more appropriate to see marihuana as the cause of the problem here than it is to see repetitive hand-washing as the cause of obsessive-compulsive disorder. The individual may be brought to psychiatric attention because of the hand-washing, but the therapy will address the underlying disorder. Becoming attached to *cannabis* is not so much a function of any inherent psychopharmacologic property of the drug as it is emotionally driven by the underlying psychopathology. Success in curtailing *cannabis* use requires dealing with that pathology.

MEDICINAL USES OF CANNABIS

Cannabis usage as a medicament is ancient, and it has included indications for headache (64,65), other types of pain (66), obstetric and gynecologic conditions (67), and psychiatric disorders (68,69).

The history of *cannabis* as a Western medicine begins in 1839, with a publication by W. B. O'Shaughnessy, a British physician working in Calcutta (70). He reported on the analgesic, anticonvulsant, and muscle relaxant properties of the drug. His paper generated a good deal of interest, and there followed more than 100 other papers in the Western medical literature from 1840 to the turn of the century. In the nineteenth century the drug was widely prescribed in the Western world for various ailments and discomforts, such as coughing, fatigue, rheumatism, asthma, delirium tremens, migraine headache, and painful menstruation. Although its use was already declining somewhat because of the introduction of synthetic hypnotics and analgesics, it remained in the United States Pharmacopoeia until 1941. The difficulties imposed on its use by the Marihuana Tax Act of 1937, as well as quality-control issues with uncertain supplies, completed its medical demise, and, from that time on, physicians allowed themselves to become ignorant about the drug.

The greatest advantage of *cannabis* as a medicine is its unusual safety. The ratio of lethal dose to effective dose is estimated on the basis of extrapolation from animal data to be about 20,000:1. Huge doses have been given to dogs without causing death, and there is no reliable evidence of death caused by *cannabis* in a human being. *Cannabis* also has the advantage of not disturbing any physiologic functions or damaging any body organs when it is used in therapeutic doses. It produces little physical dependence or tolerance; there has never been any evidence that medical use of *cannabis* has led to habitual use as an intoxicant.

Whole *cannabis* preparations have the disadvantages of instability, varying strength, and insolubility in water, which makes it difficult for the drug to enter the bloodstream from the digestive tract. The multitude of ingredients found in *cannabis* is also an opportunity, because it suggests the manufacture of different cannabinoids, synthetic or natural, with properties useful for particular purposes; some of these have now become available (66,71). One that is presently legally available for the treatment of nausea and vomiting of cancer chemotherapy and the acquired immune deficiency syndrome (AIDS) weight loss syndrome is dronabinol (Marinol), a synthetic THC. While it is not as useful medicinally as whole smoked marihuana, it is legally available as a Schedule III drug. Smoking generates quicker and more predictable results because it raises THC concentration in the blood more easily and predictably to the needed level. Also, it may be hard for a nauseated patient in chemotherapy to take oral medicine. But many patients dislike smoking or cannot inhale (69). Alternative-dosing approaches are discussed in several references (4,72–75).

There are many anecdotal reports of marihuana smokers using the drug to reduce postsurgery pain, headache, migraine, menstrual cramps, phantom limbs, and other kinds of pain. It is the case that *cannabis* acts by mechanisms different from those of other analgesics through the endocannabinoid pain mechanisms (66), and that *cannabis* may be more effective than opiates in neuropathic pain states. Again, some new synthetic derivatives might prove useful as an analgesic, but this is not an immediate prospect.

Because of reports that some people use less alcohol when they smoke marihuana, *cannabis* has been proposed as an adjunct to alcoholism treatment, but so far it has not been found useful (76–78). Most alcoholics neither want to substitute marihuana nor find it particularly helpful. But there might be some hope for use of marihuana in combination with disulfiram (Antabuse) (76). Certainly a *cannabis* habit would be preferable to an alcohol habit for anyone who could not avoid dependence on a drug but who was able to substitute one drug for another.

Approximately 20% of epileptic patients do not get much relief from conventional anticonvulsant medications. *Cannabis* has been explored as an alternative, at least since a case was reported in which marihuana smoking, together with the standard anticonvulsants phenobarbital and diphenylhydantoin (Dilantin), was apparently necessary to control seizures in a young epileptic man (79). Recent reports support the role of THC endocannabinoids in modulation of seizure threshold (80,81). Cannabidiol also demonstrates anticonvulsant properties (7,82). In one controlled study, cannabidiol in addition to prescribed anticonvulsants produced improvement in seven patients with grand mal seizures; three showed great improvement.

Of eight patients who received a placebo instead, only one improved (83).

Marihuana also reduces muscle spasm and tremors in some people who suffer from spastic disorders, including multiple sclerosis (84,85), cerebral palsy, and various causes of hemiplegia and quadriplegia, such as spinal cord injury or disease. Anecdotal reports of the use of *cannabis* for the relief of asthma abound. The antiasthmatic drugs that are available all have drawbacks—limited effectiveness or side effects. Because marihuana dilates the bronchi and reverses bronchial spasm, *cannabis* derivatives have been tested as antiasthmatic drugs. Smoking marihuana would probably not be a good way to treat asthma because of chronic irritation of the bronchial tract by tars and other substances in marihuana smoke, so recent research has sought a better means of administration. THC in the form of an aerosol spray has been investigated extensively (59,60). Other cannabinoids, such as cannabinol and cannabidiol, may be preferable to THC for this purpose. An interesting finding for future research is that cannabinoids may affect the bronchi by means of a different mechanism from that of the familiar antiasthmatic drugs. A promising new medical use for *cannabis* is treatment of glaucoma, the second leading cause of blindness in the United States. About a million Americans suffer from the form of glaucoma (wide angle) treatable with *cannabis*. Marihuana causes a dose-related, clinically significant drop in intraocular pressure that lasts several hours in both normal subjects and in those with the abnormally high ocular tension produced by glaucoma. Oral or intravenous THC has the same effect, which seems to be specific to *cannabis* derivatives rather than simply a result of sedation. *Cannabis* does not cure the disease, but it can retard the progressive loss of sight when conventional medication fails and surgery is too dangerous (86). A recent comprehensive review supports the use of cannabinoids as antioxidant protective agents in the development of vascular retinopathy of glaucoma, a process independent of intraocular pressure (87).

It remains to be seen whether topical use of THC or a synthetic cannabinoid in the form of eyedrops will be preferable to smoking marihuana for this purpose. So far THC eyedrops have not proved effective, and in 1981, the National Eye Institute announced that it would no longer approve human research using these eyedrops (76). Studies continue on certain synthetic *cannabis* derivatives and other natural cannabinoids (87). Smoking marihuana is a better way of titrating the dose than is the taking of an oral cannabinoid, and most patients seem to prefer it. Unfortunately, many patients, especially elderly ones, dislike the psychoactive effects of marihuana.

Cannabis derivatives have several minor or speculative uses in the treatment of cancer, and one major use. As appetite stimulants, marihuana and THC may help to slow weight loss in cancer patients (88), as they have in AIDS patients (55). THC has also retarded the growth of tumor cells in some animal studies, but results are inconclusive, and another *cannabis* derivative, cannabidiol, seems to increase tumor growth (89). Possibly cannabinoids in combination with other drugs will turn out to have some use in preventing tumor growth. THC may promote apoptosis (programmed cell death) in some malignant cells (90). Limonene, a monoterpenoid component of *cannabis* resin, has similar activity on breast tumor cells (91). But the most promising use of *cannabis* in cancer treatment is the prevention of nausea and vomiting in patients undergoing chemotherapy. About half of patients treated with anticancer drugs suffer from severe nausea and vomiting. In 25% to 30% of these cases, the commonly used antiemetics do not work (69). The nausea and vomiting are not only unpleasant, but are a threat to the effectiveness of the therapy. Retching can cause tears of the esophagus and rib fractures, prevent adequate nutrition, and lead to fluid loss.

The antiemetics most commonly used in chemotherapy are prochlorperazine (Compazine) and the newer ondansetron (Zofran) and granisetron (Kytril). The suggestion that *cannabis* might be useful arose in the early 1970s when some young patients receiving cancer chemotherapy found that marihuana smoking, which was, of course, illegal, reduced their nausea and vomiting. In one study of 56 patients who got no relief from standard antiemetic agents, 78% became symptom free when they smoked marihuana (92). Previously unpublished state studies of smoked *cannabis* have demonstrated 70% to 100% relief of vomiting in some 748 chemotherapy patients (93).

Several of the most urgent medical uses of *cannabis* are for the treatment of the nausea and weight loss suffered by many AIDS patients. The nausea is often a symptom of the disease itself and a side effect of some of the medicines (particularly azidothymidine [zidovudine or AZT]). For many AIDS patients the most distressing and threatening symptom is cachexia. Marihuana will retard weight loss in most patients and even helps some regain weight (69).

A committee of the Institute of Medicine of the National Academy of Sciences remarked in a report in 1982 (28, p. 139):

> *Cannabis* shows promise in some of these areas, although the dose necessary to produce the desired effect is often close to one that produces an unacceptable frequency of toxic [undesirable] side effects. What is perhaps more encouraging... is that *cannabis* seems to exert its beneficial effects through mechanisms that differ from those of other available drugs. This raises the possibility that some patients who would not be helped by conventional therapies could be treated with *cannabis*.... It may be possible to reduce side effects by synthesizing related molecules that could have a more favorable ratio of desired to undesired actions; this line of investigation should have a high priority.

The committee recommended further research, especially in the treatment of nausea and vomiting in chemotherapy, asthma, glaucoma, and seizures and spasticity.

Under federal and most state statutes, marihuana is listed as a Schedule I drug: high potential for abuse, no

currently accepted medical use, and lacking in accepted safety for use under medical supervision. It cannot ordinarily be prescribed and may be used only under research conditions. *Cannabis* was recently legalized for medical use in Canada and Holland, and liberalization of laws is proceeding in the United Kingdom and elsewhere in Western Europe.

The potential of *cannabis* as a medicine is yet to be realized, partly because of its reputation as an intoxicant, ignorance on the part of the medical establishment, and legal difficulties involved in doing the research (94). Recreational use of *cannabis* has affected the opinions of physicians about its medical potential in various ways. When marihuana was regarded as the drug of African Americans, Mexican Americans, and Bohemians, doctors were ready to go along with the Bureau of Narcotics, ignore its medical uses, and urge prohibition. For years the National Organization for the Reform of Marijuana Laws and other groups have been petitioning the government to change this classification. Now that marihuana has become so popular among a broad section of the population, we have been more willing to investigate its therapeutic value. Recreational use now spurs medical interest instead of medical hostility.

It is estimated that more than 70 million Americans have used *cannabis* and more than 10 million use it regularly. They use it not because they are driven by uncontrollable "reefer madness" craving, as some propaganda would lead us to believe, but because they have learned its value from experience. Yet almost all of the research, writing, political activity, and legislation devoted to marihuana has been concerned only with the question of whether it is harmful and how much harm it does. The only exception is the growing resurgence of interest in its usefulness as a medicine. But medicine represents only one category of marihuana use. The rest are sometimes grouped under the general heading of "recreational," but that is hardly an appropriate word to describe the many serious reasons for which people have learned to use *cannabis*. For example, many writers and artists have found that the *cannabis* high can be a catalyst to their creativity (95). Allen Ginsberg, writing while stoned, eloquently put it this way: "... the marihuana consciousness is one that, ever so gently, shifts the center of attention from habitual shallow purely verbal guidelines and repetitive secondhand ideological interpretations of experience to more direct, slower, absorbing, occasionally microscopically minute, engagement with sensing phenomena during the high moments or hours after one has smoked" (96). While many artists have learned to use *cannabis* as an aid to their creativity, many other users have discovered its capacity to catalyze the generation of ideas and insights, heighten the appreciation of music and art, or deepen emotional and sexual intimacy. (The reader who wishes to learn more about this is referred to the Uses of Marijuana Web Site [www.marihuana-uses.com], a collection of essays written by marihuana users who have found this drug useful as an enhancer of various capacities and experiences.)

This "enhancement" capacity is often underappreciated—not only by nonusers, but also by some users, especially young people who are primarily interested in promoting sociability and fun. Most of marihuana's powers of enhancement are subtle and not as immediately available as its capacity to lift mood or improve appetite and the taste of food. Many, if not most, people do not achieve a *cannabis* high during their first attempt or attempts because they have yet to learn to recognize the subtle changes in consciousness that comprise the marihuana experience. Similarly, the ability to make use of *cannabis* consciousness as an enhancer of various capacities appears to require both experience in achieving this state and learning how to make use of it.

The potential dangers of marihuana when taken for pleasure and enhancement, and its possible usefulness as a medicine are historically and practically interrelated issues—historically, because the arguments used to justify public and official disapproval of recreational use have had a strong influence on opinions about its medical potential; practically, because the more evidence accumulates that marihuana is relatively safe even when used as an intoxicant, the clearer it becomes that the medical requirement of safety is satisfied. Most recent research is tentative, and initial enthusiasm for drugs is often disappointed after further investigation. But it is not as though *cannabis* were an entirely new agent with unknown properties. Studies done during the past 10 years confirm a centuries-old promise. With the relaxation of restrictions on research and the further chemical manipulation of *cannabis* derivatives, this promise will eventually be realized. The weight of past and contemporary evidence will probably prove *cannabis* to be valuable in a number of ways as a medicine.

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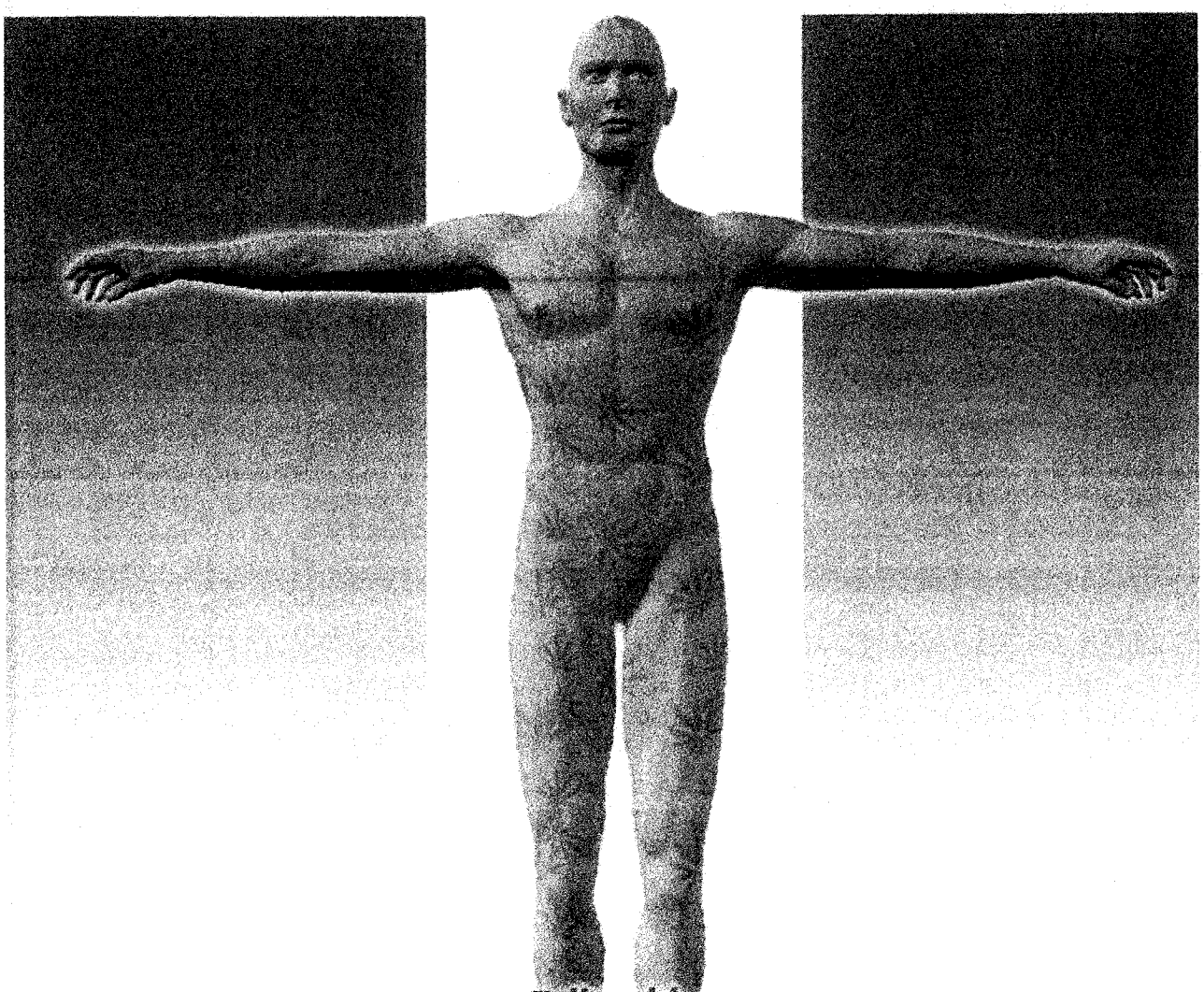
ENDOCANNABINOIDS

The Brain and Body's Marijuana and Beyond



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15 Neuropsychiatry: Schizophrenia, Depression, and Anxiety

Ester Fride and Ethan Russo

CONTENTS

INTRODUCTION

An association between cannabis use and neuropsychiatric conditions is of major importance because of the potential for the use of cannabis as a recreational drug or medicine and also for understanding the biological mechanisms by which cannabinoids act on brain structure and function. In this chapter we review evidence for a number of hypotheses which have been proposed to describe the putative role of cannabis use in the precipitation of psychosis. The majority of studies support the *vulnerability hypothesis*, especially with respect to schizophrenia. The hypothesis that the consumption of cannabis is a form of *self-medication* for the symptoms of schizophrenia and depression has also gained support.

Evidence for and against long-term neuropsychiatric impairment due to cannabis consumption has to be considered, keeping in mind both the time interval between cannabis use and the neuropsychological assessments and the age of onset of cannabis use.

Finally, recent progress in the investigation of the role of the endocannabinoid–CB_1 receptor system in mental disease in animal models as well as in humans, especially with respect to its interaction with the dopamine neurotransmitter system, opens up new avenues for the understanding and treatment of the major mental disorders.

The history and science of cannabis and cannabinoids and their relation to mental health and disease are fraught with controversy, ambivalence, and contradictory claims. Perhaps this is inevitable when one considers that endocannabinoids serve a modulatory function in many neurochemical and psychopharmacological processes, and deficiencies or excesses in any of these may produce manifestations of psychopathology. The different aspects of this controversy regarding the role of cannabis in psychiatric disorders have been reviewed previously in detail

(Grinspoon, 1977; Grinspoon and Bakalar, 1997; Grinspoon, Bakalar, and Russo, 2005; Russo, 2001; Russo, 2004; Russo et al., 2001).

HISTORICAL HIGHPOINTS

The first well-documented description of the effects of cannabis on mood may derive from Mesopotamia (see Figure 15.1). Clay tablets discovered in the Assyrian library of Ashurbanipal seem to derive from Sumerian and Akkadian documents of the 22nd century B.C.E., wherein cannabis is described as being ingested as a remedy for grief or "depression of spirits" (Thompson, 1949).

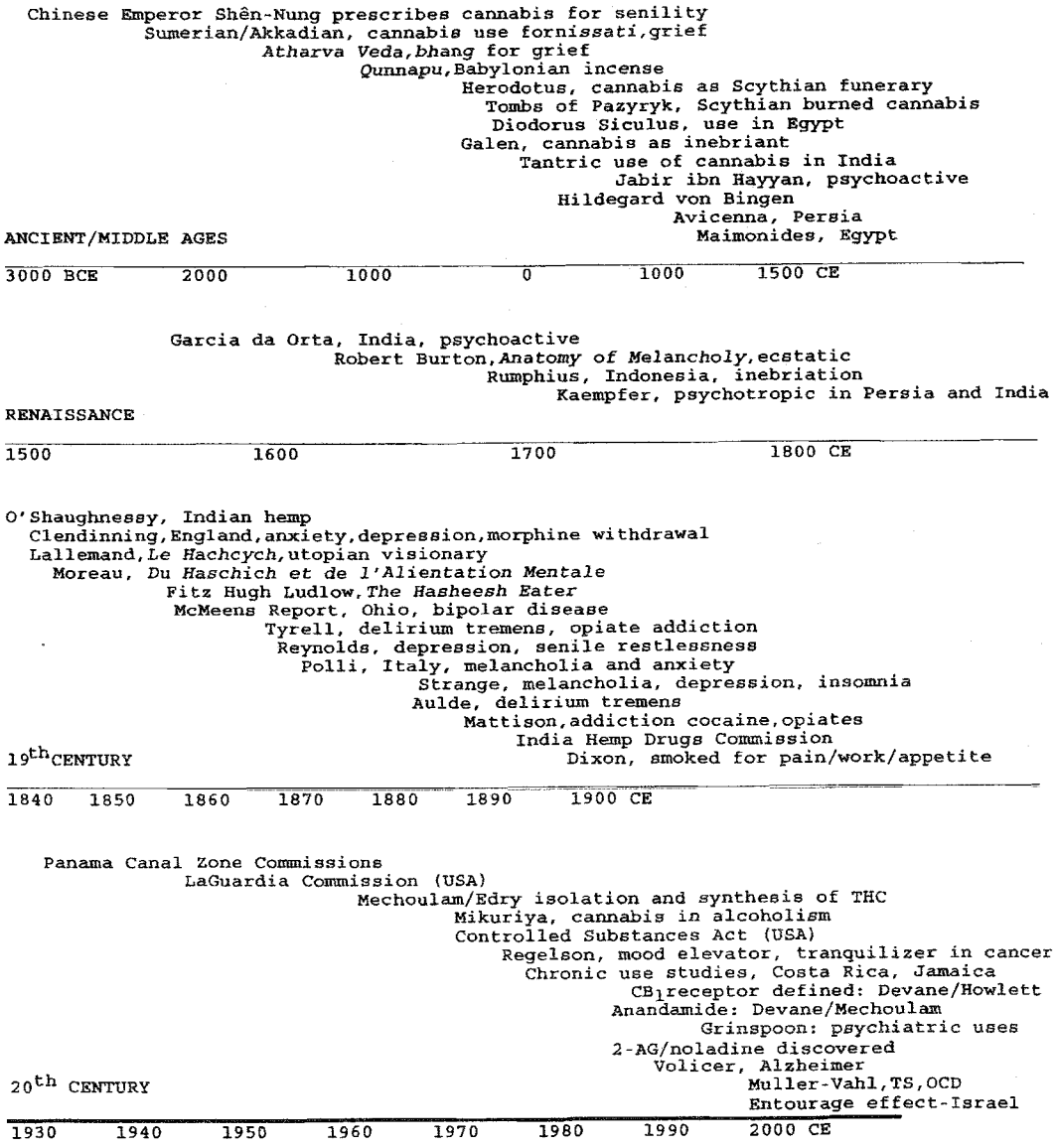

FIGURE 15.1 Cannabis Psychiatric Time Line by Ethan Russo, M.D. (Adapted and expanded from Russo, 2004.)

In the Indian *Atharva Veda* (passage 11,6,15) circa 1600 B.C.E., cannabis, or *bhanga*, is one of five herbs employed to "release us from anxiety." (Commission, 1894, Appendix 3, p. 286).

Perhaps older yet is the *Pên Tsao Ching*, written in the first or second century but attributed to Emperor Shên Nung in the third millennium B.C.E., which noted that excessive ingestion of cannabis flowers produced hallucinations (literally, "seeing devils") (Li, 1974, p. 446).

The Greek historian Herodotus noted the use of burned cannabis flowers in the 5th century B.C.E. by the Scythian peoples of central Asia as a funerary rite causing them to "shriek with delight at the fumes" (Herodotus, 1998, p. 259, Book 4, Passage 75).

Hyperbole has often surrounded any discussion of cannabis, and this is true even in the early accounts of its dangers: Al-Ghazzi, quoting Az-Zarkashi in the 14th century, indicated that cannabis "causes sudden death or madness" (Hamarneh, 1978, p. 288), although he acknowledged its therapeutic role in medicine.

The benefits of Indian hemp in depression were noted in Europe by the 17th century (Burton, 1907) but were not studied more formally until the 19th. Jacques-Joseph Moreau investigated cannabis both as a model psychosis-inducing and psychotherapeutic agent (Moreau, 1845). In North America in 1859, McMeens (1860) described a case study of a man with "hysterical insanity" who had cycles of manic energy during which he thought himself a great inventor. These were interspersed with bouts of melancholy and inertia — symptoms of what we would likely recognize today as bipolar disease. A tincture of *Cannabis indica* seemed to even his mood, presaging similar anecdotal evidence of such benefit noted by Grinspoon in modern-day bipolar patients (Grinspoon and Bakalar, 1998).

Controversy continued, however, and led to the first in-depth governmental investigation by the British that resulted in the Indian Hemp Drugs Commission Report (Indian Hemp Drugs Commission, 1894), which exceeded 3000 pages in length. The commission scoured the asylums of the subcontinent to assess the widely assumed role of cannabis as a precipitant of mental illness. It was observed that documentation was poor, and attribution to *ganja* was often assigned arbitrarily in cases where no other explanation was forthcoming (Kaplan, 1969). No actual association of cannabis and mental illness was apparent, and only 61 cases in the entire region were identified in which the herb could be etiologically implicated. Equivalence of symptomatology was observed in cases with or without such exposure, and affliction associated with cannabis usage appeared to be self-limiting. In contrast in Egypt, one author felt that hashish was a frequent cause of insanity (Warnock, 1903), but this was not based on any epidemiological investigation.

Another extensive evaluation was undertaken in India (Chopra and Chopra, 1939) in which the authors noted the prevalent usage of cannabis as a stress reliever and accessory to hard physical labor. They even acknowledged a benefit in individuals suffering from hypochondriasis or neurosis. They summarized the issue of etiological causation of mental illness as follows (p. 103): "It does not necessarily produce insanity except in perhaps those who have predisposition to it."

After extensive study, the LaGuardia Commission noted (Wallace and Cunningham, 1944, p. 218): "Furthermore, those who have been smoking marihuana for a period of years showed no mental or physical deterioration which may be attributed to the drug."

In Morocco, a "cannabis psychosis" was noted among *kif* smokers (Benabud, 1957), but (see Grinspoon, Bakalar, and Russo, 2005) its purported incidence (5/1000) is well below the baseline rate of schizophrenia in this and other populations worldwide.

THE LAST 40 YEARS

The widespread use of cannabis in western industrial nations began in the 1960s and led the National Institute on Drug Abuse (NIDA) to fund an extensive series of studies on the chronic use of cannabis in nations with such experience. In Jamaica (Rubin and Comitas, 1975), chronic ganja use was studied in 30 users and matched controls. One nonuser showed signs of depression on neuropsychological testing and another was assessed to be a borderline case of depression. No signs of active

psychosis were observed. In all, no significant differences were observed between the groups with respect to mood, thought, or behavior.

In Greece, hashish smokers were studied (Stefanis et al., 1977), and though a greater incidence of psychopathology was observed in users as compared to controls, most were accounted for by "personality disorders." Interestingly, more psychiatric abnormalities were observed in moderate as opposed to heavy users. In Costa Rica (Carter, 1980), cannabis smokers believed it to be of benefit for depression and malaise. No significant indicators of adverse sequelae were observed in the personality or performance of cannabis users.

More recently, studies have attempted to test several distinct hypotheses about the relationship between cannabis use and psychiatric disease. By far, the majority have dealt with schizophrenia and only a minority with depression and anxiety. In general, the following hypotheses were investigated:

1. Cannabis use causes psychosis.
2. Cannabis use precipitates a psychotic attack in vulnerable individuals.
3. Cannabis use worsens (positive) schizophrenic symptoms.
4. Cannabis use is comorbid with schizophrenia.
5. Cannabis is used as self-medication for the negative symptoms of schizophrenia.
6. Cannabis is used as self-medication for anxiety and depression.

Before discussing the evidence for and against these hypotheses, a separate but relevant issue which has remained unresolved for over a 100 yr (Iversen, 2000) must be discussed: Does cannabis induce (symptoms of) schizophrenia, or does the drug induce a separate entity (marijuana psychosis, [MP]) of psychotic symptoms that persist well after its consumption?

Nunez and Gurpegui (2002) compared spontaneous attacks of schizophrenia (acute schizophrenia) to chronic, heavy cannabis-use–induced schizophrenia (MP). Although there was a partial overlap of the symptoms, the symptoms of MP and acute schizophrenia could be distinguished from each other. Moreover, all MP patients completely recovered with neuroleptic treatment. Therefore, the findings of this study argue for the existence of MP as a separate disorder.

In two studies on healthy subjects (Dumas et al., 2002; Skosnik et al., 2001), schizotypic traits were compared among three groups: nonusers, regular current users, and an intermediate group consisting of past or occasional users. In both studies, regular use was associated with schizotypal personality traits. In the study by Dumas and colleagues, occasional and past users were similar to regular users, whereas, in contrast, in the study sample of Skosnik et al., past cannabis users were similar to nonusers. In the Skosnik study, the intermediate group included only past users (i.e., with no cannabis use for at least 45 d prior to assessment), whereas in the Dumas study, the intermediate group included occasional as well as past users; when data from both studies are combined, the findings argue against a residual effect of cannabis and are consistent with the position that MP is simply an expression of increased vulnerability to cannabis-induced intoxication (Nunez and Gurpegui, 2002). It should be noted, however, that "past users" in the Skosnik study may have included light or one-time users, who are not at risk of developing MP.

Whether or not MP is a separate psychotic entity, the effect of cannabis use on the onset and development of schizophrenia has been widely investigated but still remains controversial.

A variety of research designs have been used to investigate the cannabis–psychoses association, including retrospective *vs.* prospective designs, clinical *vs.* nonclinical, and with small *vs.* large samples. In these studies, timing is critical in two respects: (1) Were the symptoms measured during, immediately after, or long after cessation of cannabis use? and (2) What was the age of onset of cannabis use? Despite the widely different approaches, the findings of the majority of the studies support at least some association between cannabis smoking and psychosis.

Grinspoon studied 41 patients in Massachusetts with first-break acute schizophrenia (Grinspoon, 1977); six (15%) had a history of cannabis use. Upon close examination, he found that in four

patients, the development of psychosis was quite remote from the exposure. The role, if any, of cannabis in the remaining two patients was quite unclear.

In a recent study from Sweden on schizophrenia (Zammit *et al.*, 2002), the authors reexamined Swedish conscripts from 1969, the same cohort studied earlier by Andreasson et al., (1987). In the current study, the group defined as the "frequent users" (> 50 times) was found to have an incidence of schizophrenia of 5.7% as opposed to 0.6% in nonusers of cannabis. These cannabis smokers reportedly had not used any other drug.

Another recent study examined a cohort of young New Zealanders for cannabis use and the development of adult psychosis (Arsenault et al., 2002). In this article, the controls were defined as those who had used cannabis 0 to 2 times, whereas "cannabis users" were those who had taken the drug 3 times or more by age 15 and continued at some unspecified rate of intake through age 18. Smoking cannabis was found to increase the incidence of psychosis in adults, and importantly, psychosis was more likely the earlier the age of onset of cannabis use. This age of onset was also determined to be relevant in a study by Nunez and Gurpegui (2002), who found that in heavy cannabis users who developed MP, a large proportion (64%) had started to smoke cannabis between the ages of 13 and 15.

In another study and its follow-up, performed on 232 schizophrenia patients, 13% of which had a history of cannabis use, the relationship between the age of onset of cannabis smoking and the onset of schizophrenia was analyzed (Hambrecht and Hafner, 2000; Buhler et al., 2002). Although the distinction between cannabis use and drug (other than alcohol) use was not clearly defined, the authors estimated that the great majority (88%) of the drug users predominantly but not solely used cannabis. It appeared that whereas overall drug or cannabis use was twice as high in the study sample as in the general population of that area (Germany), the cannabis users with schizophrenia in the study group could be divided into equal groups of: (1) those with a history of having used cannabis for years before the onset of psychosis; 2) those in whom cannabis use and schizophrenia started at the same time, and 3) those who had commenced cannabis use only after the onset of schizophrenia. Therefore, these observations support the causation, the vulnerability, as well as the self-medication hypotheses (see following text). A recent evaluation of the data (Degenhardt and Hall, 2002) indicates support for the concept that cannabis may serve as a precipitant in vulnerable patients and increase relapse rates.

On the other hand, evidence for a causal relationship between cannabis use and psychoses in otherwise low-risk persons is much more scarce (Johns, 2001; Hall and Degenhardt, 2000; Mass et al., 2001). Convincingly arguing against the causation hypothesis is the finding that in Australia no increased rate of incidence of schizophrenia has been reported over a period of several decades despite a dramatic increase in cannabis use during that period (Degenhardt, Hall and Lynskey, 2003).

In agreement with this, Joy, Watson, and Benson (1999) of the Institute of Medicine observed (p. 106) that "people with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from the use of cannabinoids," and "there is little evidence that cannabis alone produces a psychosis that persists after the period of intoxication."

Interestingly, in a cohort at very high risk for schizophrenia (defined by the presence of subthreshold psychotic symptoms and a family history of schizophrenia), no relationship was found between cannabis use and the incidence of schizophrenia (Phillips et al., 2002). Is it possible that the likelihood of developing schizophrenia was already so high that cannabis use could not add to the final outcome?

In support of the self-medication hypothesis, it is known that cannabis may ameliorate certain symptoms of psychosis (Warner et al., 1994), including activation symptoms and the subjective complaints of depression, anxiety, insomnia, and pain. In a sample of patients with chronic schizophrenia, Bersani and colleagues (2002) found evidence for a precipitating influence of cannabis in the development of schizophrenia, and in the same sample, a subgroup was identified that used cannabis to self-medicate for amelioration of negative symptoms. This finding is supported by observations in a nonclinical sample of a significant association between cannabis use and the negative symptoms of schizophrenia (Verdoux et al., 2003).

The proposition that cannabidiol (CBD), a nonpsychoactive component of the cannabis plant, possesses considerable antipsychotic activity (Zuardi and Guimaraes, 1997) is supportive of the self-medication role of cannabis in the disorder, but this action is not via the cannabinoid CB_1 receptor.

Taken together, most studies confirm the vulnerability hypothesis for cannabis use and schizophrenia. Thus, schizophrenia patients should probably not use cannabis because a psychotic episode can be induced in someone with a preexisting disorder and, indeed, increased hospitalization rates and symptom exacerbation have been demonstrated (Caspari, 1999). Increased rates of psychosis are also observed in those meeting the criteria for cannabis dependence (Fergusson, Horwood, and Swain-Campbell, 2003). Hollister, (1986) summarized in his review (p. 6–7): "It would seem reasonable to assume that cannabis might unmask latent psychiatric disorders."

MOOD DISORDERS

An acute depressive reaction, occasionally observed in cannabis users, has most often been encountered in those with underlying depression (Grinspoon and Bakalar, 1997). The same authors, however, have published several case reports of improvement in bipolar symptoms with cannabis usage (Grinspoon and Bakalar, 1998). These clinical observations are partly supported by epidemiologic investigations which have approached the question (analogous to the questions on etiology in schizophrenia; see section titled "The Last 40 Years") of whether cannabis use increases the risk for depression or, conversely, whether depression results in more frequent use of cannabis in an attempt to self-medicate. Cross-sectional studies tend to suggest that depression induces cannabis use, and longitudinal (prospective) studies suggest the opposite, i.e., that cannabis consumption precipitates depression in later life (up to a fourfold increase in risk) (Bovasso, 2001; Patton et al., 2002). However, in nonclinical samples, no association or very weak associations were found between various measures of depression and cannabis smoking (Chen et al., 2002; Green and Ritter, 2000; Tournier et al., 2003). Suicide attempts were significantly higher in cannabis smokers but this association lost statistical significance after sociodemographic factors, history of psychiatric symptoms in childhood, and concurrent psychiatric symptoms were controlled (Beautrais et al., 1999).

Thus, taken together, the epidemiological evidence does not support a causative or precipitating role for cannabis in chronic anxiety or depression. With respect to self-medication, among four patients with serious chronic diseases (in the Compassionate Use Investigational New Drug Program) who utilized high amounts of cannabis daily for many years for symptom control (Russo et al., 2002), scores on the Beck Depression Inventory were very low. Similarly, of the 2480 patients surveyed who had used cannabis for medical indications in one large practice in California over a number of years, 660 (26.6%) did so primarily for treatment of mood disorders; this included 162 (6.5%) for depression, 73 (3%) for anxiety, 34 (1.4%) for bipolar disorder, and even 26 (1%) for schizophrenia (Gieringer, 2001).

Although there are no reports of controlled clinical trials on the use of cannabis for mood disorders, benefits have been noted in depression measures in cancer patients treated with THC (Regelson et al., 1976). In addition, CBD has demonstrated benefit in the treatment of anxiety (Zuardi and Guimaraes, 1997), allaying anxiety in experimental subjects with no significant side effects (Zuardi et al., 1993). Controlled clinical trials seem indicated with this agent. Interestingly, a recent study on rats, in which extinction of cocaine- or amphetamine-induced place preference, a form of motivational learning, was enhanced, suggests that CBD may be involved in emotion-relevant processes (Parker et al., 2003).

EFFECTS OF LONG-TERM CANNABIS USE ON COGNITION AND BEHAVIOR

A major concern with long-term use of cannabis, whether consumed for recreational or medicinal purposes, is the possibility of irreversible damage to brain structure or function. There is agreement among researchers, however, that long-term use of cannabis does not result in structural brain damage

or gross cognitive deficits (Solowij, 2002). However, the possibility that cannabis use results in subtle and/or specific cognitive impairments has been the subject of considerable controversy.

Hall and Solowij (1998) have reported detrimental neurocognitive effects in long-term heavy cannabis users. However, these subjects were investigated while they were current users and therefore the deficits could have been a direct effect of intoxication. Until recently, no studies were available which observed a period of abstinence of more than a few days (Solowij, 2002). In an additional study performed by Solowij and colleagues (2002), very long-term cannabis users (median 24 yr of use) showed deficits in tests for memory and attention. However, users defined as short-term users, but whose mean duration of use was nevertheless 10.2 yr, did not differ, in general, from controls. Moreover, abstinence intervals were minimal (median 17 h). As recovery of function is likely to involve changes in plasticity, such as CB_1 receptor densities, such a short interval is unlikely to allow for significant reversals.

More recently, investigations have been performed which allowed for considerably longer abstinence periods (1 to 3 months). These investigations in general do not support the existence of a residual effect of cannabis that persists well after cessation of consumption. Thus, in a long-term prospective investigation of a sample of children of mothers who smoked cannabis during pregnancy (Fried et al., 2002), these children themselves became heavy users as young adults, displaying a 4-point decrease in IQ (as compared to an earlier assessment made at the age of 9–12 yr). In contrast, heavy users who had abstained from cannabis use for at least 3 months gained IQ points, which was similar to the findings in light current users or nonusers: these groups gained 3.5, 5.8, and 2.6 points respectively. In a study by Pope and colleagues (2001), a 28-d-long wash-out period was sufficient to eliminate the deficits in neuropsychological performance observed in current heavy users. It is possible, however, that a more detailed analysis of cognitive function would reveal residual effects of cannabis smoking. Perhaps future studies will more definitively answer this question.

In accordance with the latter two investigations, a recent meta-analytic study of residual neurocognitive effects of cannabis use did not reveal detrimental effects, except for a modest impairment in memory tests. The authors conclude that when medical use of cannabinoids is being considered, the health benefits should be carefully weighed against the very modest potential for cognitive decline (Grant et al., 2003).

A meta-analytic study of 3206 subjects on the behavioral traits associated with cannabis use and abuse (Gorman and Derzon, 2002) demonstrated merely an association with "unconventionality" and not more serious disorders, mirroring much older observations (Goode, 1970). Cannabis use and good mental health are not mutually exclusive. A recent British study has shown that drug experimentation is associated with high self-esteem (Regis, 2001). Another British study showed no causal relationship between cannabis use and delinquency in young people (Hammersley et al., 2003).

In short, chronic cannabis use does not appear, after cessation of drug use, to result in a significant cognitive decline or behavioral symptomatology. However, as discussed for cannabis use as a risk factor for schizophrenia (see section titled "The Last 40 Years"), age of onset of cannabis use may be critical in determining the outcome of cannabis consumption later in life. Thus, in a recent study by Pope and colleagues (2003), heavy cannabis users who had started before the age of 17 differed from controls in neuropsychological tests, mainly on verbal IQ.

BIOLOGICAL EVIDENCE FOR A ROLE OF THE ENDOCANNABINOID–CB_1 RECEPTOR SYSTEM IN NEUROPSYCHIATRIC DISORDERS

The prefrontal cortex (PFC) is thought to integrate cognitive and emotional functions and, as the target area for the mesocortical dopamine system, may be the primary dysfunctional area in schizophrenia and the site of action for antischizophrenic drugs (Thierry et al., 1978). This area is also exquisitely responsive to stress (Thierry et al., 1976), and it is well established that schizophrenia

is frequently triggered by stressful life events (Carlson, 2001). The density of CB_1 receptors in the PFC is high, at least relative to other G-protein-coupled receptors (Herkenham et al., 1990). Close interactions between the dopamine system and exo- and also endocannabinoids have been shown repeatedly. For example, THC was shown to increase presynaptic dopamine efflux and utilization in the PFC (Chen et al., 1990; Jentsch et al., 1997). In the dorsal striatum also, an interaction has been observed but in the opposite direction: activation of D_2 dopamine receptors caused increased outflow of anandamide (Giuffrida et al., 1999).

A link between stress and cannabinoids has also been shown repeatedly. Thus, administration of cannabinoids or anandamide produced anxiety-like responses in rats (Rodriguez de Fonseca et al., 1997; Navarro et al., 1997) and mice (Chakrabarti et al., 1998) and activation of the hypothalamic–pituitary–adrenal "stress hormone" axis in rats (Weidenfeld et al., 1994; Rodriguez de Fonseca et al., 1996) and calves (Zenor et al., 1999). We have shown that acute noise stress induces a fourfold increase in anandamide levels in the PFC but not in the hippocampus of adult mice (Fride and Sanudo-Pena, 2002). Taken together, these studies suggest that activation of the endocannabinoid–CB_1 receptor system in the PFC, either by stress or by cannabis use, may trigger symptoms of schizophrenia.

Thus far, only a few studies have been performed on the putative connection between the endocannabinoid–CB_1 receptor system and schizophrenia in humans. Higher concentrations of CB_1 receptors have been found in the dorsolateral PFC of deceased schizophrenic patients but not in other regions such as the hippocampus and the caudate-putamen (Dean et al., 2001). Levels of anandamide were higher in the cerebrospinal fluid of schizophrenic patients, but only in 3 out of 10 patients (Leweke et al., 1999). In the same study, an elevation of the non-CB_1 receptor-binding palmitoyl ethanol amide was also found in a subset of 4 of the 10 patients. It seems that only an analysis of both these findings combined produced statistical significance (Leweke et al., 1999). Further, healthy volunteers intoxicated with cannabis resin displayed perceptual abnormalities similar to that of schizophrenic patients who did not receive cannabis (Emrich et al., 1997). This observation was interpreted as support for the hypothesis that schizophrenia is characterized by a disturbance of the endocannabinoid–CB_1 receptor system. Taken together these preliminary findings support the possibility that schizophrenia may be characterized by an overactive endocannabinoid–CB_1 receptor system in the PFC. Fritsche (2000) has hypothesized that CB_1 receptor-deficient (knockout) mice may display similarities to patients with schizophrenia and may be a model for the disease, implying that schizophrenia is characterized by a lack of CB_1 receptors. Although much more work needs to be done, the data emanating from various approaches largely point to a major role for the endocannabinoid–CB_1 receptor system in schizophrenia, in close interaction with the dopamine neurotransmitter system.

CONCLUSIONS

Cannabis has been used in medicine and psychiatry for many centuries and in a variety of cultures. A role for cannabis in the etiology and precipitation of mental disease has been frequently suggested and has obtained wide support. However, the nature of this influence has remained controversial. Most research has focused on schizophrenia. The vulnerability hypothesis, according to which, in individuals at risk for psychosis, cannabis use may trigger the disease, has obtained extensive support. A simple causative effect by which cannabis use may induce schizophrenia in otherwise normal individuals is hardly tenable. The theory that consuming cannabis is an effort to self-medicate, mainly for the negative symptoms of schizophrenia, has also gained some support and remains an attractive hypothesis, especially in view of the biological evidence for an intimate connection between the endocannabinoid–CB_1 receptor system, the dopamine neurotransmitter system, stress, and schizophrenia.

Although most of the evidence does not support the existence of adverse effects persisting beyond the cessation of long-term cannabis use, it seems that when cannabis consumption is started

at a young (teen or preteen) age, it may be prudent to exercise more caution, although current data are far from clear. Both a greater vulnerability to schizophrenia as well as claims of possible permanent cognitive damage have been reported in such young "starters." Finally, the dramatic progress which has been made over the last decade in unraveling the mechanisms by which the cannabinoids affect brain function, both as a healing agent and as a detrimental factor, will open new avenues for their medical application and for understanding the impact of cannabis use in neuropsychiatry.

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